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Budesonide
A Preliminary Review of its Pharmacodynamic Properties and Therapeutic Efficacy in Asthma and Rhinitis

S.P. Clissold and *R.C. Heel*

ADIS Drug Information Services, Auckland

Various sections of the manuscript reviewed by: *G.M. Cochrane*, Department of Thoracic Medicine, Guy's and New Cross Hospitals, London, England; *R. Dahl*, Department of Pulmonary Diseases, Århus Kommunehospital, Århus, Denmark; *A.M. Henriksen*, Department of Paediatrics, Århus University Hospital, Århus, Denmark; *K.T. Jackson* Laboratory of Otolaryngology, Emory University School of Medicine, Atlanta, Georgia, USA; *A.B. Kay*, Department of Allergy and Clinical Immunology, The Cardiothoracic Institute, London, England; *J. Morrison-Smith*, Penyraber, Fishguard, Wales; *H. Mygind*, University ENT Department, Rigshospitalet, Copenhagen, Denmark; *J.J. Rohrsdder*, Pulmonary Disease Section, Veterans Administration Medical Center, Phoenix, Arizona, USA; *J.H. Toogood*, Allergy Clinic, Victoria Hospital, London, Ontario, Canada; *J.O. Warner*, Brompton Hospital, London, England; *M.H. Williams*, Pulmonary Division, Department of Medicine, Albert Einstein College of Medicine of Yeshiva University, Bronx Municipal Hospital Center, New York, USA; *J.D. Wilson*, Department of Immunobiology, School of Medicine, University of Auckland, New Zealand.

Contents

Summary

Synopsis: *Budesonide*[1] *is a non-halogenated glucocorticosteroid which has been shown to possess a high ratio of topical to systemic activity compared with a number of reference corticosteroids such as beclomethasone dipropionate, flunisolide, and triamcinolone acetonide. It appears to undergo extensive first-pass metabolism to metabolites of minimal activity which accounts for the low level of systemic activity.*

The majority of therapeutic trials in asthma have been of short term duration and have demonstrated that conventional doses of inhaled budesonide (200 to 800 μg/day) and beclomethasone dipropionate (400 to 800 μg/day) are of similar efficacy in both adults and children with moderate to severe asthma. Other studies have compared high doses of inhaled budesonide (400 to 3200 μg/day in 4 divided doses) with both alternate day (7.5 to 60mg) and daily (7.5 to 40mg) oral prednisone in patients with severe or unstable asthma. In the small number of such trials to date, inhaled budesonide was superior to prednisone with respect to the level of asthma control and the lesser influence on adrenal function. Long term open studies have similarly shown that inhaled budesonide can be gradually substituted for oral prednisone in steroid-dependent patients, often with a concomitant improvement in pulmonary function and asthma control.

Intranasal budesonide (200 to 400 μg/day) relieves nasal symptoms in patients with seasonal allergic, perennial allergic and vasomotor rhinitis. In comparative studies in patients with seasonal rhinitis it has been shown to be of similar efficacy as intranasal flunisolide and intranasal beclomethasone dipropionate and superior to intranasal sodium cromoglycate (cromolyn sodium) and the antihistamine dexchlorpheniramine.

Following inhalation, the most commonly reported side effects have been: candidiasis, dysphonia and sore throat, while after intranasal administration the most frequent adverse reactions have been nasal stinging, throat irritation, dry nose and slight nasal bleeding. At usual dosages, both formulations of budesonide appear to have little or no effect on adrenal function.

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Thus, at this stage in its development budesonide has been shown to offer an effective alternative to oral or other inhaled corticosteroids in the management of asthma and rhinitis. However, its relative efficacy and tolerability during long term use, compared with beclomethasone dipropionate, remains to be clarified.

Pharmacodynamic Studies: In animals budesonide has a high ratio of topical to systemic activity compared with reference corticosteroids such as beclomethasone dipropionate, flunisolide and triamcinolone acetonide. In man, budesonide was shown to have 1.6 to 3 times greater local anti-inflammatory activity using a skin vasoconstriction assay, and between 2 and 4 times less systemic activity than beclomethasone dipropionate. The reduction in systemic potency in healthy volunteers should augur well for the clinical usefulness of budesonide, and trials in patients with asthma have not revealed any significant differences between conventional doses of budesonide and beclomethasone dipropionate. In practice, usual doses of inhaled or intranasal budesonide have caused only minimal changes in hypothalamic-pituitary-adrenal (HPA) function, although a dose-response relationship with plasma cortisol concentrations has been documented. When inhaled therapy was substituted for oral prednisolone there was a gradual increase in plasma cortisol concentrations, highlighting the lower adrenal suppressive activity of budesonide compared with oral steroid.

Even after single doses, inhaled budesonide produced a rapid improvement in pulmonary function in patients with asthma, characterised by a dose-response relationship with peak expiratory flow rate. A divided daily regimen gave a more pronounced and longlasting increase in lung function at a reduced total daily dosage compared with a single daily dose.

The mechanism of action of budesonide, like that for other glucocorticoids, remains obscure. However, it has been noted that as long as pretreatment was sufficiently long, inhaled budesonide inhibited both the immediate and late reactions provoked by bronchial allergen challenge. Similarly, intranasal budesonide inhibited the type I-mediated immediate nasal reaction and this may be related to suppression of histamine release in nasal biopsy samples *in vitro*.

Following intranasal administration of budesonide for up to 1 year in patients with rhinitis, no adverse morphological changes in the nasal mucosa occurred. However, no studies evaluating the histological characteristics of the bronchial mucosa after inhaled budesonide have been reported.

Pharmacokinetic Studies: In man, peak plasma concentrations of uncharged budesonide occurred within 1 hour of inhalation and approximately 3 hours after oral ingestion, thus reflecting the rapid rate of absorption from the lung. Systemic bioavailability was calculated to be 10.7% after oral administration, with evidence of extensive first-pass metabolism.

The volume of distribution of budesonide is comparatively large (301L), which is indicative of wide tissue distribution. Budesonide has been shown to be extensively bound to plasma proteins (88.3%) with negligible binding to transcortin. The relatively short elimination half-life (approximately 2 hours) and high plasma clearance (83.7 L/hour) highlight the rapid systemic elimination of budesonide. *In vitro* studies have corroborated the involvement of the liver in the rapid biotransformation of budesonide; 2 major metabolites with minimal activity have been isolated and identified. Only trace amounts of budesonide are excreted unchanged in the urine.

Therapeutic Trials: The majority of clinical trials with inhaled budesonide have been crossover studies designed to evaluate the effectiveness of different dosage regimens, or its comparative efficacy with that of inhaled beclomethasone dipropionate. Most were of short duration (2 to 4 weeks) and, when peak expiratory flow rate was measured, demonstrated a dose-response relationship over a wide range of inhaled dosages (160 to 1600 μg/day in divided doses) in patients with moderately severe and severe (steroid

dependent) asthma. The dose-response relationship was maintained whether budesonide was administered twice or 4 times daily.

In short term comparative trials inhaled budesonide (400 to 3200 μg/day in 4 divided doses) was found to be superior to alternate-day oral prednisone (7.5 to 60mg) in patients with moderate to severe asthma, and was able to produce as effective control of unstable asthma as daily oral prednisone (7.5 to 40mg once daily). In this latter study, at doses producing equivalent control of the asthmatic condition, inhaled budesonide had significantly less effect on adrenal function. In other comparative trials, inhaled budesonide (200 to 800 μg/day) was of approximately equal efficacy as inhaled beclomethasone dipropionate (400 to 800 μg/day) in both adults and children with asthma. In long term open trials gradual substitution of inhaled budesonide for oral steroid has often resulted in an improvement in pulmonary function and asthma control. Oral steroid dosage was usually markedly decreased during budesonide administration, and 1600 μg/day of inhaled budesonide reduced mean oral prednisone usage by half.

Intranasal budesonide has been used in the treatment of seasonal allergic, perennial allergic and vasomotor rhinitis. In seasonal rhinitis doses of 200 to 400 μg/day were significantly better than placebo in relieving nasal symptoms and reducing the need for supplemental antiallergy medication, but had no effect on eye symptoms. In patients with seasonal allergic rhinitis, intranasal budesonide was as effective as intranasal beclomethasone dipropionate and intranasal flunisolide, and significantly superior to both intranasal sodium cromoglycate and the oral antihistamine dexchlorpheniramine. Short term comparisons in patients with perennial rhinitis, with or without an allergic component, have shown budesonide to be significantly better than placebo in relieving nasal symptoms when doses of 200 to 400 μg/day were administered. In long term open trials in patients with perennial rhinitis, intranasal budesonide (200 to 400 μg/day) has consistently produced a significant reduction in all nasal symptoms with a low incidence of mild and transient side effects.

In patients with nasal polyposis, budesonide was significantly more effective than placebo in reducing total symptom scores and increasing nasal peak flow rates, while rhinoscopy revealed a distinct decrease in nasal congestion, a decrease in polyp size, and a significant reduction in the number of polyps. However, only 10 patients received the active drug in this study and a well-designed trial in a greater number of patients is required to confirm the usefulness of intranasal budesonide in this condition.

Side Effects: Generally, budesonide has been well tolerated and few trials have reported adverse reactions associated with treatment. However, the majority of these studies have been of short term duration (2 to 4 weeks). Longer term trials in greater numbers of patients are required to fully evaluate the tolerability of budesonide.

Using the inhaled preparation, the most commonly reported side effects have been oropharyngeal candidiasis, hoarseness and sore throat, as is also the case with other inhaled corticosteroids. The reported incidence of candidiasis varied widely among studies, but was reduced by using a spacing device or by reverting to a less frequent dosing regimen. Gradual substitution of inhaled budesonide for oral prednisolone resulted in a number of side effects such as hoarseness, sore throat, arthralgia, myalgia, exacerbation of eczema and pulmonary eosinophilia and sarcoidosis, which can all be explained in terms of a local reaction or are indicative of systemic corticosteroid withdrawal. Administration of inhaled budesonide, up to 800 μg/day, appears to have a minimal effect on adrenal function as assessed by basal plasma cortisol concentrations and their increase after tetracosactrin stimulation. Nevertheless, during substitution of inhaled budesonide for oral corticosteroid, recovery of hypothalamic-pituitary-adrenal integrity can take up to 12 months after long term oral steroid therapy, and it is essential to take special care during this period.

Intranasal budesonide has been well tolerated, and in both long and short term trials in patients with rhinitis the most common side effects have been local reactions such as nasal stinging, throat irritation, dry nose and nasal bleeding. In comparative studies,

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intranasal budesonide has produced fewer adverse effects than the antihistamine dexchlorpheniramine, significantly less nasal irritation than flunisolide, and equivalent incidences of minor transient reactions as intranasal beclomethasone dipropionate and intranasal sodium cromoglycate. No evidence of adrenal suppression has been reported with this formulation.

Dosage and Administration: The inhaled dose of budesonide for the treatment of asthma in adults should be individualised. The recommended initial dose is 400 to 1600 μg/day divided into 2 or 4 administrations. The maintenance dose is usually 200 to 400 μg/day – using the lowest dose that leaves the patient symptom free. In children with asthma the recommended dose is 200 to 400 μg/day, divided into 2 or 4 administrations.

In the treatment of rhinitis the recommended dosage is 100μg (2 actuations of 50μg each) into each nostril morning and evening (400 μg/day). This dosage can be halved once a good response has been achieved.

1. Pharmacodynamic Studies

Budesonide is a non-halogenated glucocorticosteroid which is structurally related to 16α-hydroxyprednisolone (Thalén and Brattsand, 1979) [fig. 1]. The drug is a 1 : 1 mixture of 2 epimers, designated 22R and 22S (Aherne et al., 1982; Roth et al., 1980; Thalén and Brattsand, 1979; Wikby et al., 1978), which were initially considered to have similar pharmacological activity. However, more recent evidence suggests that the 22R epimer is 2 to 3 times more potent than the 22S epimer and has a different pharmacokinetic profile. The clinical usefulness of inhaled and intranasal corticosteroids in the treatment of asthma and rhinitis is well accepted but their exact mechanism of action remains to be established. A high ratio of local anti-inflammatory to systemic activity appears to be an important indicator relating therapeutic efficacy to systemic tolerability, and the increased ratio for budesonide compared with other glucocorticoids might be expected to offer an advantage in this regard.

1.1 Topical and Systemic Glucocorticoid Activity

Using the human skin vasoconstriction assay to estimate local anti-inflammatory activity, budesonide was more potent than the 5 other corticosteroids investigated (Johansson et al., 1982c) [fig. 2]. Employing the same test, budesonide has been shown to be as active as betamethasone dipropionate and more potent than betamethasone valerate, desonide, flunisolide, hydrocortisone butyrate and the acetonides of fluocinolone, prednacinolone and triamcinolone (Brattsand et al., 1982c,d; Gruvstad and Bengtsson, 1980; Johansson et al., 1982a,b). A comparison between budesonide and its 2 epimers indicated an order of topical activity of 22R > budesonide > 22S, with the 22R epimer approximately twice as potent as the 22S epimer (Brattsand et al., 1982c). Compared with beclomethasone dipropionate, budesonide has been shown to be approximately 1.6 to 3 times more active when applied topically (Johansson et al., 1982b,c).

The systemic glucocorticoid activity of budesonide, as determined by changes in plasma cortisol and total or differential white blood cell count in healthy volunteers, was 2 to 4 times less than that of beclomethasone dipropionate following oral administration, and it was also significantly less active after inhalation – although the disparity between the 2 drugs was less pronounced (Johansson et al., 1982c; Löfdahl et al., 1984) [fig. 3]. Following a single intravenous infusion of ^{3}H-budesonide 500μg to 6 healthy male volunteers, total white blood cell count and lymphocyte count were transiently decreased, while the neutrophil count was increased after 4 hours (Ryrfeldt et al., 1984).

During the 8-hour study, the eosinophil count

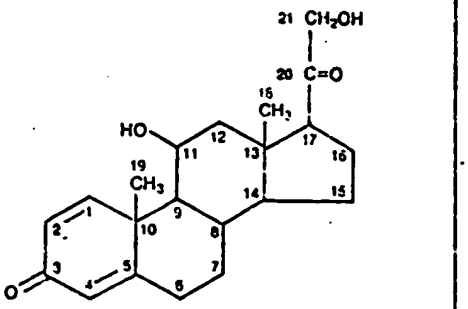

Fig. 1. Structural formulae of 16α-hydroxyprednisolone and budesonide in its 2 epimeric forms.

was reduced from 135 to 111/mm³ after placebo and from 246 to 77/mm³ after budesonide, but there were no statistically significant differences between the 2 groups. In contrast, plasma cortisol concentrations were slightly but significantly ($p < 0.05$) suppressed 4 and 8 hours after budesonide administration compared with placebo values. In a comparison with oral prednisolone, the systemic potency (as assessed by depression of plasma cortisol) of 1.0mg of inhaled budesonide was equivalent to 5mg of oral steroid, while 3.2mg of inhaled budesonide was approximately 2 times more potent than 5mg of oral prednisolone (Johansson et al., 1982b).

Animal studies confirm the increased ratio of topical to systemic activity of budesonide compared with a number of glucocorticoids such as beclomethasone dipropionate, flunisolide, fluocinolone acetonide, and triamcinolone acetonide (Brattsand et al., 1982b,c,d; Thalén and Brattsand, 1979; Thalén et al., 1984). Using a recently developed model assessing local anti-inflammatory activity in the lung, budesonide instilled intratracheally or given by inhalation counteracted the pathophysiological changes (bronchial and interstitial infiltration of eosinophils and mononuclear cells) associated with the intratracheal administration of 'Sephadex' beads (Brattsand et al., 1983). Furthermore, local administration of budesonide produced a time-dependent inhibition of bradykinin-induced inflammation in hamster cheek pouches (Svensjö and Roempke, 1984). In addition, budesonide and its 2 epimers have been shown to have

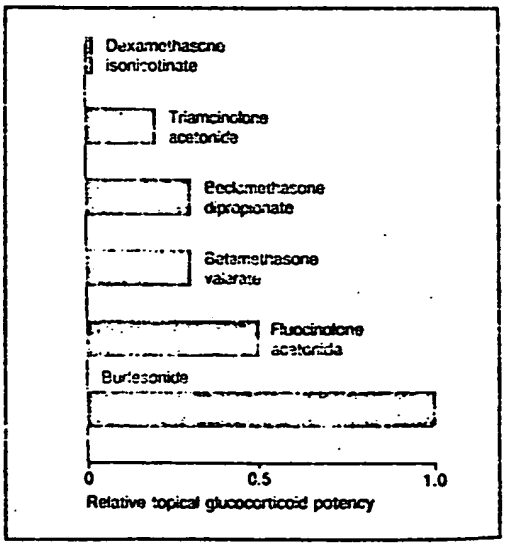

Fig. 2. Relative topical potency (area under the time-effect curve) of various glucocorticoids using the human skin vasoconstriction assay in 12 healthy volunteers (after Johansson et al., 1982c).

a high affinity for the glucocorticoid receptor in rat skeletal muscle and this closely correlated with high topical glucocorticoid activity *in vivo* (Dahlberg et al., 1984).

1.2 Effect on Haematological Parameters

Systemic prednisone produces an increase in blood neutrophils and a decrease in blood basophils, eosinophils and lymphocytes within 4 to 8 hours of intravenous administration to healthy volunteers (Saavedra-Delgado et al., 1980). These effects have generally returned to, or are returning to, normal within 24 hours, and a similar transient lymphopenia has been noted following oral administration of prednisone to steroid-dependent asthmatic patients (Chiang et al., 1980).

In healthy subjects, single doses (200, 800 and 3200μg) of inhaled budesonide and beclomethasone dipropionate decreased the number of lymphocytes and eosinophils and increased the number of neutrophils, without significantly affecting the number of monocytes (Johansson et al., 1982c). The 2 drugs were also given orally (2, 4 and 8mg), and in both studies beclomethasone dipropionate had a significantly greater effect on the white cell response than did budesonide.

In contrast to these findings in volunteers, treatment with aerosol budesonide (200μg twice daily) for 4 weeks did not significantly alter any of the haematological parameters measured in patients with chronic asthma (Willey et al., 1982). Similarly, an equal daily dose of beclomethasone dipropionate 100μg 4 times a day did not affect the majority of parameters measured, although there was a tendency ($p > 0.05 < 0.1$) to increase total white cell count and a small but significant reduction ($p < 0.05$) in the number of neutrophils. Further studies in patients with asthma have shown that neither inhaled budesonide 400 to 3200 μg/day nor oral prednisone 7.5 to 60mg on alternate days significantly altered the total blood eosinophil count compared with a baseline of beclomethasone dipropionate 800 μg/day alone or combined with prednisone (15mg on alternate mornings) in steroid-dependent patients (unpublished data on file, Astra). However, a dose-dependent reduction in total blood eosinophils in patients with asthma was reported by Toogood et al. (1982b), although significant suppression was only observed when inhaled doses of budesonide were relatively high – 800 and 1600 μg/day in patients dependent and not dependent upon oral prednisone, respectively.

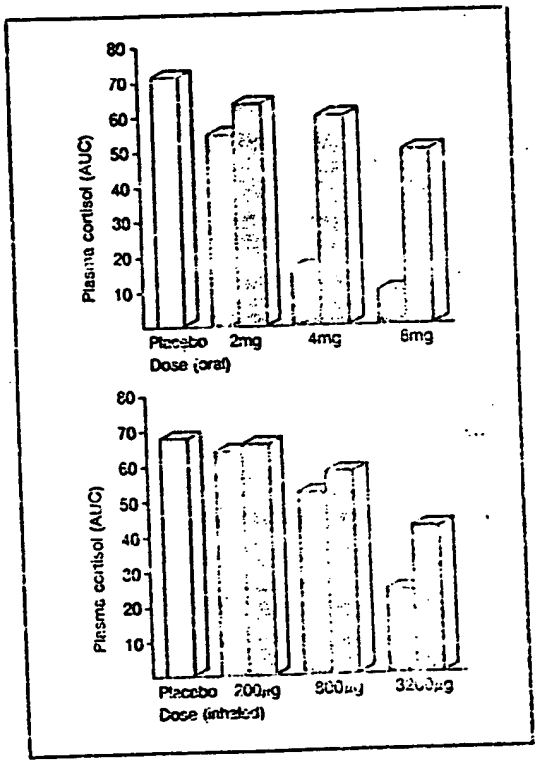

Fig. 3. Plasma cortisol (area under the curve) in healthy subjects after oral administration (n = 8) and inhalation (n = 12) of budesonide □ and beclomethasone dipropionate ⊠ (after Johansson et al., 1982c).

1.3 Effect on Adrenal Function

Resting early morning plasma cortisol concentrations, and those after tetracosactrin (synthetic ACTH) stimulation, provide useful information concerning the state of the hypothalamic-pituitary-adrenal (HPA) axis in asthmatic patients (Webb,

1983). Significant reductions in plasma cortisol have seldom been observed using usual inhaled doses of beclomethasone dipropionate and betamethasone valerate (British Thoracic and Tuberculosis Association, 1975), flunisolide (Spangler et al., 1979) or triamcinolone acetonide (Bernstein et al., 1982). Of the inhaled corticoids, beclomethasone dipropionate has been the most extensively studied, and in 2 recent reviews (Brogden, 1983a; Brogden et al., 1984) daily doses of 400 to 2000μg have been shown to cause some adrenal suppression in adult patients. In the majority of trials there has been a general improvement in adrenal function following the substitution of inhaled beclomethasone dipropionate for oral steroids, especially when oral treatment was on a once daily schedule. Recently, however, a less marked or no improvement has been observed following changeover from alternate-day oral steroids to inhaled beclomethasone dipropionate (Toogood, 1979; Wyatt et al., 1978).

As noted previously (section 1.1), budesonide administered orally and by inhalation was significantly less potent than equal doses of beclomethasone dipropionate in lowering plasma cortisol concentrations in healthy subjects (fig. 3). Greatly increased inhaled doses of budesonide (2400, 4800 and 7200 μg/day) and beclomethasone dipropionate (1500, 3000 and 4500 μg/day) both produced a dose-dependent decrease in morning serum cortisol concentrations in 12 healthy volunteers (Löfdahl et al., 1984). The dose-response curves ran parallel, and the results indicate that inhaled budesonide, at these high doses, possesses only 60% of the relative systemic activity of inhaled beclomethasone dipropionate. In patients with asthma, however, little or no adrenal suppression was noted with usual dosages of the 2 steroids (Björkander et al., 1982; Willey et al., 1982), and at high dosages both budesonide (1600 μg/day) and beclomethasone dipropionate (1500 μg/day) produced similar reductions of morning plasma cortisol (Ebden and Davies, 1984). In these studies, neither drug affected the cortisol response to tetracosactrin stimulation. Substitution of inhaled budesonide (up to a mean of 1060 μg/day) for oral prednisolone in 30 steroid-dependent severely asthmatic patients over a period of 1 year induced a concomitant increase in plasma cortisol concentrations; this highlights the lower adrenal suppressive action of budesonide compared with oral prednisolone (Rosenhall et al., 1982b).

In a short term trial (2-week crossover), inhaled budesonide dosages of 400, 800 and 1600 μg/day were compared in 34 chronic asthmatics and a dose-dependent decrease in serum cortisol was observed (Toogood et al., 1982b). The reduction in serum cortisol was significantly different from baseline values at doses of 800 and 1600 μg/day in prednisone-dependent patients but only at a daily dosage of 1600μg in patients not dependent on prednisone. It was also noted that morning-only treatment with high doses of budesonide tended to conserve hypothalamic-pituitary-adrenal (HPA) responsiveness but at the cost of a slight reduction in efficacy. In a similar study, a significant decrease in serum cortisol was only revealed at a daily budesonide dose of 3200μg in prednisone users and no significant suppression of serum cortisol was documented for non-prednisone users at daily budesonide doses of 400 to 1600μg (unpublished data on file, Astra).

The cortisol response to tetracosactrin stimulation in 7 asthmatic children was normal after 4 weeks' treatment with aerosol budesonide 400 μg/day (Henriksen and Dahl, 1983). Similarly, in 27 children with severe asthma requiring inhaled steroid therapy, neither budesonide (400 μg/day) nor beclomethasone dipropionate (400 μg/day) significantly altered basal cortisol concentrations or the response to tetracosactrin stimulation after 4 weeks' therapy (Field et al., 1982). More recently, 24-hour urinary cortisol excretion was not significantly changed in 12 asthmatic children treated with inhaled budesonide (400 μg/day with a spacer) for 3 weeks (Henriksen, 1984).

Intranasal budesonide 50 to 800 μg/day, used in the treatment of perennial or seasonal rhinitis for periods of 2 weeks to 1 year (section 4), did not suppress adrenal function as indicated by a lack of change in serum cortisol (Balle et al., 1980; Lindqvist et al., 1982, 1983; Malm et al., 1981;

Norman et al., 1984; Steensen and Lindqvist, 1981), the response of plasma cortisol to tetracosactrin stimulation (Balle, 1982; Lindqvist et al., 1982, 1983; Pipkorn and Berge, 1983), or in the excretion of urinary 17-hydroxycorticosteroids (Norman et al., 1984).

1.4 Effect on Antigen-Induced Reactions

Many factors relating to the pathogenesis of asthma can be explained in terms of the known biological activity of mast cell-derived mediators, whether they are released as a result of specific IgE/allergen interactions or as the result of nonspecific mechanisms (Kay, 1983). It has been suggested that the events associated with bronchial obstruction may be divided into 3 stages: a rapid spasmogenic phase, a late sustained phase and a subacute/chronic inflammatory phase.

1.4.1 Effect on Bronchial Allergen Challenge

Early studies with beclomethasone dipropionate and sodium cromoglycate (cromolyn sodium) indicated that whereas the latter agent in doses of 20 to 40mg inhibited both the immediate and delayed types of asthmatic reaction, only the late reaction was prevented by beclomethasone dipropionate (Breslin et al., 1973; Pepys et al., 1974). In a more recent study, however, it has been shown that 1 week's pretreatment with beclomethasone dipropionate (400 or 800 μg/day) by pressurised aerosol or dry powder inhalation inhibited the immediate asthmatic reaction induced by appropriate antigen challenge in approximately 50% of asthmatic patients (Burge, 1982).

The effects of budesonide on the 'dual' allergen-induced asthmatic response have been reported in 3 clinical trials (Dahl and Johansson, 1982b,c; Tivenius et al., 1982). In the most comprehensive study (Dahl and Johansson, 1982c), both the immediate and delayed responses to bronchial allergen challenge were evaluated after 12 hours, 1 week and 1 month of pretreatment with inhaled budesonide (fig. 4). The immediate asthmatic reaction (as indicated by percentage fall in peak expiratory flow rate) was increasingly reduced by the longer periods of budesonide pretreatment, whereas the attenuation of the late allergic reaction was less affected by duration of therapy because of the almost complete blocking of this response during short term treatment.

1.4.2 Effect on Nasal Allergen Challenge

Initial studies with beclomethasone dipropionate 200μg suggested that the immediate reaction to nasal allergen challenge was not inhibited by brief periods (up to 2 days) of intranasal pretreatment (Pelikan and Pelikan-Filipek, 1982). However,

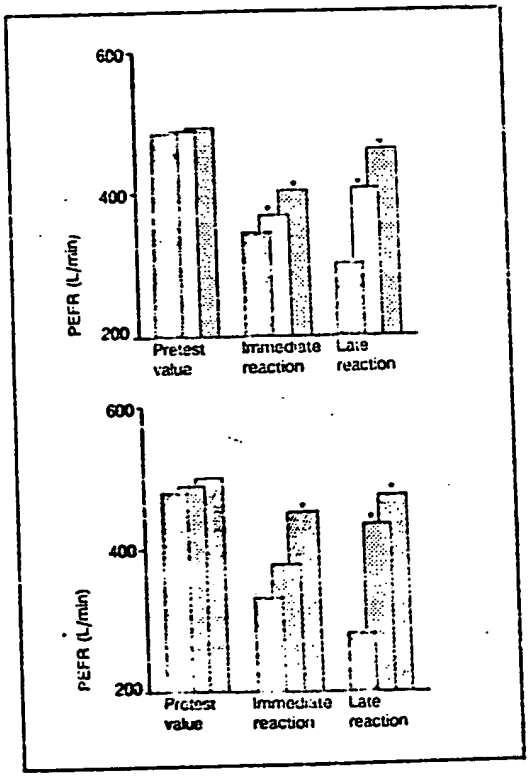

Fig. 4. Comparison of various periods of budesonide pretreatment (□ = 12 hours; ▨ = 1 week; ▩ = 1 month) on a control bronchial challenge test (■) in 10 patients known to exhibit a dual bronchial reaction. Pretest peak expiratory flow rates (PEFR) and maximal, immediate, and late responses to allergen challenge were all recorded; * = significantly different from control values (after Dahl and Johansson, 1982).

longer periods of pretreatment (1 week) have shown a clear inhibitory effect on pollen-induced allergic type I reactions, as indicated by inhibition of nasal blockage (Vilsvik et al., 1975).

Both placebo and budesonide (100, 400 and 1600μg) administered 3 hours before allergen challenge significantly reduced the fall in nasal peak flow, number of sneezes and nasal secretion in 12 patients with asymptomatic seasonal allergic rhinitis, while after 1 week's pretreatment (twice daily administration) only budesonide produced a further significant decrease in sneezing and secretion and a significant increase in nasal peak flow (Munch et al., 1982). Similarly, in a double-blind placebo-controlled crossover study in 13 patients with out-of-season allergic rhinitis, 1 week's pretreatment with intranasal budesonide (50 or 200μg twice daily) significantly inhibited the allergen-induced type I reaction (Pipkorn, 1982a,c).

Employing a repeat protocol in virtually the same group of patients, pretreatment with intranasal budesonide had a minimal effect on histamine-induced nasal symptoms (Pipkorn, 1982b) and the results indicate that the effect of budesonide on the immediate type I reaction cannot be attributed to a blocking of histamine's activity at the receptor level, but more likely, inhibit its release from sensitised cells. In addition, a detectable concentration of histamine in the nasal mucosa of healthy subjects and patients with allergic rhinitis has been documented and, despite the study taking place out of season, patients with rhinitis had higher histamine concentrations than healthy subjects (Pipkorn and Andersson, 1982). Following 1 week's pretreatment with intranasal budesonide, the increased nasal mucosa histamine concentration in 22 patients with rhinitis was significantly reduced, and anti-IgE-induced release of histamine *in vitro* in nasal biopsy samples taken from 13 of these patients was also inhibited. Similarly, it has been shown that overnight culture of human leucocytes in the presence of budesonide (0.1 nmol/L to 1 μmol/L) inhibited anti-IgE-induced human basophil histamine release *in vitro* and the results suggested a dual mechanism of action (Bergstrand et al., 1984).

It is not clear from the study of Pipkorn and Andersson (1982) whether the effect of budesonide on mucosal histamine concentrations was mediated through a reduction in the number of cells containing histamine, a reduction in the concentration of histamine within the cell, or a combination of the two. However, no qualitative or quantitative morphological changes in mast cells were observed as a result of treatment with budesonide in 14 asymptomatic allergic rhinitis patients (Pipkorn, 1983a). Consequently, a reduction in the number of mast cells in the nasal mucosa does not appear to explain the reduced mucosal concentrations of histamine or the inhibitory effect on the immediate allergic reaction in asymptomatic allergic rhinitis patients treated with budesonide. It also seems unlikely that a direct vasoconstrictor effect, similar to the effect on the skin, can account for the inhibitory activity of intranasal budesonide since no difference was found to occur in mucosal blood flow compared with placebo in 11 healthy volunteers (Bende et al., 1983).

1.4.3 Antianaphylactic Activity

It has been shown that histamine and slow-reacting substance of anaphylaxis (SRS-A) are the main mediators of antigen-induced bronchospasm in guinea-pigs sensitised to produce IgE and/or IgG antibodies (Andersson, 1982). Studies with budesonide and beclomethasone dipropionate revealed that these 2 glucocorticoids did not protect ovalbumin-sensitised (to produce mainly IgG antibodies) guinea-pigs from anaphylactic shock following rechallenge, although both potentiated the protective effect of mepyramine in this test (Forsberg and Sörenby, 1981). Furthermore, both drugs inhibited the release of SRS-A from lung tissue *in vitro* but were without effect on the tissue content and antigen-induced release of histamine (Forsberg and Sörenby, 1981; Forsberg et al., 1982). These findings suggest that budesonide and beclomethasone dipropionate may have a beneficial effect on the immediate allergic reaction by inhibiting IgG-mediated release of SRS-A. However, using 2 sensitisation procedures that lead to the formation of predominantly IgE antibodies in one model, and

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exclusively IgG antibodies in a second model, both budesonide and hydrocortisone reduced *in vivo* anaphylactic bronchoconstriction and *in vitro* histamine release in guinea-pigs sensitised to produce predominantly IgE antibodies (Andersson and Brattsand, 1982). Additionally, *in vitro* studies have shown that pretreatment with intratracheally administered budesonide inhibits IgE-mediated release of mediators participating in both the anaphylactic and inflammatory reactions (leukotrienes B_4 and D_4, histamine and platelet activating factor) in chopped lungs taken from ovalbumin-sensitised guinea-pigs (Andersson et al., 1984). Finally, it has recently been shown that budesonide and beclomethasone dipropionate are of equal potency in inhibiting IgE-mediated bronchial anaphylaxis in guinea-pigs, but to induce systemic effects a 5- to 10-fold increase in budesonide dosage was required, indicating that it may be the more selective glucocorticoid (Andersson et al., 1983).

1.5 Effect on Bronchial and Nasal Mucosa

Long term application of potent topical corticosteroids to the skin may cause dermal atrophy and the question arises whether similar changes occur in respiratory mucosa following prolonged aerosol or intranasal administration of these agents. Studies with beclomethasone dipropionate have revealed no important changes in bronchial or nasal mucosa following long term administration (Brogden et al., 1984). However, such findings do not necessarily follow for other glucocorticoids and since budesonide has been shown to be more potent than beclomethasone dipropionate when applied topically (see section 1.1), histological assessment of mucosal changes with prolonged use would seem appropriate. In studies in patients with asthma, no evaluations of the effect of inhaled budesonide on bronchial mucosa have been reported. However, histological analysis of nasal mucosal biopsy specimens obtained from patients with rhinitis, treated for up to 1 year with intranasal budesonide, revealed no significant morphological changes in the epithelium such as metaplasia or atrophy compared with pretreatment specimens (Balle, 1982; Holopainen et al., 1982; Lindqvist et al., 1983; Pipkorn and Berge, 1983).

1.6 Acute Dose-Response Studies

The time course of response to inhaled budesonide has been assessed in double-blind, single-dose, crossover trials in patients with bronchial asthma (Dahl and Johansson, 1982d; Ellul-Micallef and Johansson, 1983a,b; Ellul-Micallef et al., 1980). Each study included 12 patients and the time course of response was evaluated by changes in peak expiratory flow rate (PEFR). When 1000μg of inhaled budesonide (via a tube spacer) and 40mg of oral prednisolone were compared with placebo, the peak increase in PEFR was noted 6 to 8 hours after administering budesonide and remained significantly increased for up to 12 hours, whereas for oral prednisolone peak increases were observed between 8 and 10 hours and they remained significantly increased for up to 27 hours (Ellul-Micallef et al., 1980). The increase in PEFR was significantly superior for oral prednisolone from 8 hours onwards.

An acute dose-response study in which 1000μg of inhaled budesonide, 125μg of subcutaneously injected terbutaline, a combination of the two, and placebo were all compared, revealed that terbutaline had a peak effect within 1 hour. An increase in PEFR was noted only 4 hours after budesonide but PEFR remained significantly increased throughout the remainder of the 8-hour study (Dahl and Johansson, 1982d). When the 2 drugs were administered simultaneously the bronchodilatory effects appeared additive, with an early increase in PEFR and a more sustained improvement in lung function for the remainder of the trial.

In another study, 3 doses of inhaled budesonide (100, 400 and 1600μg with a tube spacer) were compared with oral budesonide (1600μg) and oral prednisolone (40mg) over a 12-hour period (Ellul-Micallef and Johansson, 1983a) [fig. 5]. All inhaled doses of budesonide produced a significantly greater increase in PEFR than did oral budesonide and when the areas under the PEFR time curves (AUCs) were calculated a dose-response relationship was established. Oral prednisolone was administered 2

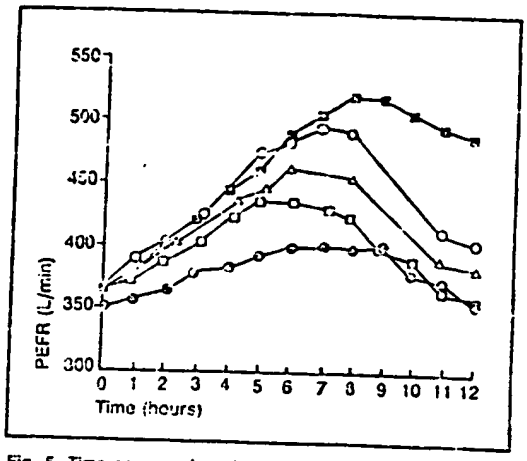

Fig. 5. Time course of peak expiratory flow rate (PEFR) response to oral prednisolone (□), oral budesonide 1600μg (○) and 3 inhaled doses of budesonide (□——□ = 100μg; Δ——Δ = 400μg; ○——○ = 1600μg) in 12 patients with bronchial asthma (after Ellul-Micallef and Johansson, 1983a).

days prior to budesonide in a single-blind comparison with placebo, in order to identify corticosteroid responders: the maximum increase in PEFR was significantly greater than that produced by the different inhaled budesonide dosages.

Using a similar protocol in a follow-up study, 2 single doses of budesonide (400 and 1600μg) were compared with a multiple-dose regimen (4 × 100μg doses at 2-hour intervals) in patients with bronchial asthma (Ellul-Micallef and Johansson, 1983b). Although the 1600μg dose resulted in the highest PEFR for the first 7 hours, from the tenth hour onwards the divided regimen was significantly superior. When the change in the AUC of PEFR was compared, there was no significant difference between 1600μg and 4 × 100μg and both were a significant improvement over the single 400μg dose of budesonide. These data highlight the importance of frequency of administration on pulmonary response (see section 3.1.3).

2. *Pharmacokinetic Studies*

There have been only a limited number of trials published in which the pharmacokinetic characteristics of budesonide have been evaluated. In most instances these studies have addressed the problem of explaining the high topical to systemic ratio of activity. However, 2 trials have been reported in which more detailed pharmacokinetic assessments were performed in human volunteers (Ryrfeldt et al., 1982) and in dogs (Ryrfeldt et al., 1979). In addition, a recent investigation studied the individual contribution of the 2 epimers of budesonide to the overall pharmacokinetic profile following intravenous administration of ^{3}H-budesonide (Ryrfeldt et al., 1984). No pharmacokinetic studies have been reported in patients with asthma or rhinitis.

2.1 Absorption

When any drug is given by metered dose inhalation only about 10% of each dose administered enters the lungs, the majority of the remainder being deposited in the mouth and subsequently swallowed (Newman, 1983). Consequently, it is important to establish the oral pharmacokinetic profile of drugs given by aerosol inhalation. In healthy male volunteers 500μg of ^{3}H-budesonide was administered orally, intravenously and by inhalation through a tube spacer (the inhaled dose was corrected for losses in the mouth and in the delivery system, and was calculated to be 200μg), and the plasma concentrations of total radioactivity and of unchanged drug were measured (Ryrfeldt et al., 1982) [fig. 6]. Following inhalation, the highest concentrations of unchanged budesonide were found in the earliest plasma samples (< 1 hour), whereas after oral administration the peak plasma concentrations of unchanged budesonide occurred after 3 hours and those of total radioactivity between 2 and 4 hours. The systemic availability of budesonide was calculated to be 10.7% following oral administration, while 73% of the dose reaching the lung was systemically available, suggesting extensive first-pass metabolism (Ryrfeldt et al., 1982).

Intratracheally instilled ^{3}H-budesonide (1 μg/lung) in isolated perfused lungs from guinea-pigs and rats reached equilibrium with the pulmonary

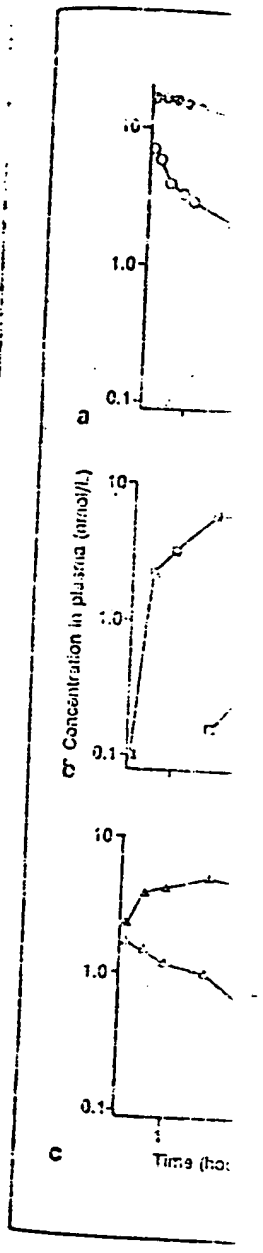

Fig. 6. Plasma concentrat
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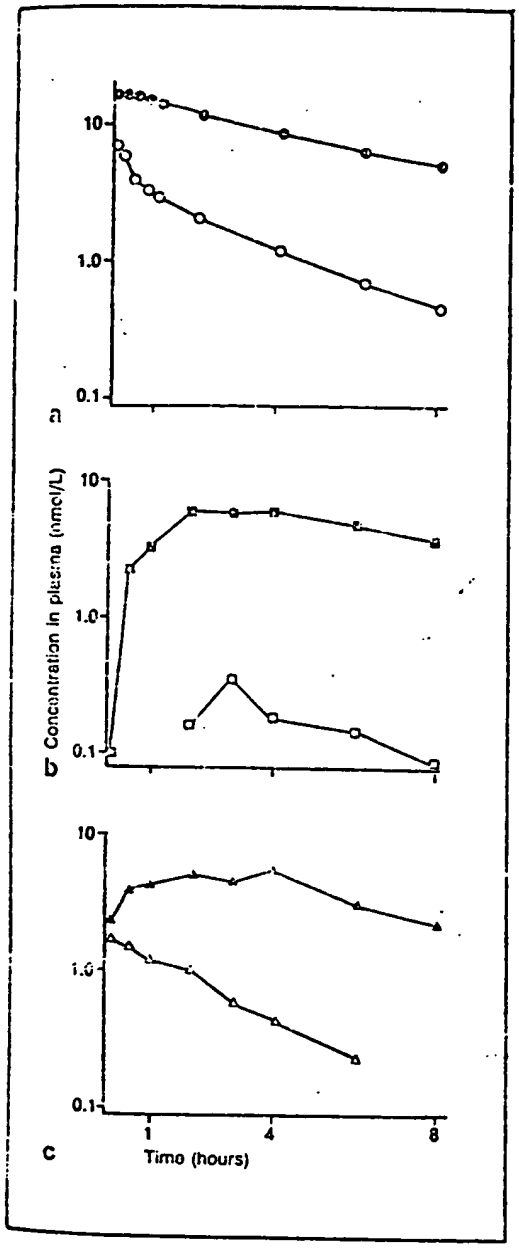

Fig. 6. Plasma concentration of total radioactivity (o □ Δ) and unchanged drug (○ □ △) following (a) intravenous, (b) oral and (c) inhalation administration of ^{3}H-budesonide 500μg to 6, 3 and 3 healthy male volunteers, respectively (after Ryrfeldt et al., 1982).

circulation within 5 minutes, illustrating the rapid absorption of budesonide solution through the mucosa and parenchyma of the lung (Brattsand et al., 1982a). When administered intratracheally as micronised particles (< 5μm) to guinea-pigs *in vivo*, the major portion of the 100μg dose (≥ 75%) disappeared from the lungs within the first 20 minutes. Polarisation microscopy indicated that local deposition and dissolution of the micronised particles may be the rate-limiting step in the overall absorption process (Brattsand et al., 1982a). More recently it has been shown that following intratracheal administration of budesonide into guinea-pig lungs *in vitro*, the uptake of budesonide epimer 22R was much greater than that of epimer 22S. Additionally, no metabolites of budesonide were detected in either lung or perfusate samples (unpublished data on file, Astra).

2.2 Distribution

Following intravenous administration of ^{3}H-budesonide 500μg to 6 healthy volunteers, the volume of distribution of unchanged drug was calculated to be 301.3L (Ryrfeldt et al., 1983). Recently, using a similar protocol, 500μg of ^{3}H-budesonide was infused intravenously in 6 healthy volunteers and the volumes of distribution of epimer 22R and epimer 22S were found to be 424.9L and 245.1L, respectively (Ryrfeldt et al., 1984). The significantly greater volume of distribution for epimer 22R may be explained by a higher tissue affinity resulting from its more hydrophobic properties.

The plasma protein binding of budesonide *in vitro* was calculated to be 88.3% by equilibrium dialysis and ultracentrifugation, with negligible binding to transcortin (Ryrfeldt et al., 1982).

2.3 Elimination

2.3.1 Metabolism

Budesonide has been shown to have a high ratio of topical to systemic activity compared with other corticosteroids such as beclomethasone dipropionate, flunisolide, fluocinolone acetonide and triam-

cinolone acetonide (see section 1.1). This difference probably depends on a more rapid rate of biotransformation in the liver (Brattsand et al., 1982b,c,d). At present there are few data currently available concerning the *in vivo* metabolic degradation of budesonide. However, various studies have evaluated the *in vitro* metabolism of budesonide in liver and skin supernatants from several species, including man. Negligible degradation of budesonide, hydrocortisone or triamcinolone acetonide occurred in skin preparations from man, rat or mouse, whereas budesonide was rapidly metabolised in liver preparations from all 3 species (Andersson et al., 1982b) [table I]. Interestingly, budesonide epimer 22R was biotransformed almost twice as quickly as epimer 22S and in a previously reported vasoconstriction assay it was found to be approximately twice as potent (Brattsand et al., 1982c). Similar *in vitro* studies indicate that budesonide is metabolised more rapidly than triamcinolone acetonide and beclomethasone monopropionate (the major step for loss of activity of beclomethasone dipropionate) in human liver preparations (Ryrfeldt et al., 1982). When rat liver preparations were used, budesonide was more rapidly degraded in homogenates from male rats than from female rats and this was reflected in a much reduced systemic potency (as assessed by thymolytic activity) for male rats *in vivo* (Andersson et al., 1982a). These results highlight the greater capacity of the male rat to metabolise drugs generally, probably caused by a higher activity of oxidative enzymes in the liver.

These findings have led a number of workers to conclude that budesonide undergoes extensive first-pass metabolism (Andersson et al., 1982a,b; Brattsand et al., 1982b,c; Ryrfeldt et al., 1979, 1982). Additional indirect evidence for this comes from the finding that the systemic potency of budesonide is increased by liver enzyme inhibition (SKF-525A) and decreased by liver enzyme induction (phenobarbitone) [Brattsand and Källström, 1983].

More recently, an in depth assessment of the metabolic degradation of budesonide was carried out in human liver homogenate *in vitro* (Edsbäcker et al., 1983). Two major metabolites identified using this technique were 6β-hydroxybudesonide and 16α-hydroxyprednisolone. When the 2 epimers of budesonide were incubated separately, no 16α-hydroxyprednisolone could be detected after incubation of the 22S epimer and this pathway therefore seems to be selective for the 22R epimer. The 2 metabolites identified *in vitro* are present also in human plasma following intravenous administration of budesonide (unpublished data on file, Astra). It has been shown that the 2 metabolites have much less glucocorticoid activity (< 1%) than budesonide (Dahlberg et al., 1984), and the possibility arises that hydroxylation of the 6β-position to form 6β-hydroxybudesonide and loss of the 16α,17α-acetal group to form 16α-hydroxyprednisolone may be the major metabolic pathways involved in the rapid biotransformation of budesonide into metabolites of low activity.

Table I. Range of *in vitro* metabolic half-lives of various glucocorticoids incubated for 30 minutes in liver supernatants prepared from man, rat and mouse (after Andersson et al., 1982b)

Glucocorticoid	Half-life (minutes)		
	man	rat	mouse
Budesonide	7-23	28-38	17-22
Budesonide epimer 22R	6-16	23-29	7-8
Budesonide epimer 22S	8-38	35-48	26-33
Hydrocortisone	40-67	14-21	82-165
Triamcinolone acetonide	13-58	161-196	21-34

2.3.2 Excretion

In 3 healthy volunteers 45% of the total dose of orally administered ^{3}H-budesonide 500μg was recovered in the urine and 29.6% in the faeces within the first 96 hours (Ryrfeldt et al., 1982). In the same study, following budesonide 500μg inhalation in 3 volunteers, 31.8% of the dose was recovered in the urine, 15.1% in the faeces, and 41.4% in the mouth or inhaler. In a recent study it was discovered that none or only trace amounts of this total was in the form of unchanged budesonide during the first 24

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From these studies, plasma clearance of unchanged budesonide was calculated to be 83.7 L/hour (Ryrfeldt et al., 1982) while the plasma clearances of epimers 22R and 22S were 116.8 and 66.7 L/hour, respectively (Ryrfeldt et al., 1984). These data highlight the rapid plasma elimination of budesonide and its 2 epimers and presumably reflect the high hepatic clearance of the compounds.

In a study of 10 healthy volunteers it was found that less than 1% of budesonide was lost in the exhaled air following inhalation, and differences in airflow and tidal volume did not affect this value (Morén and Andersson, 1980).

2.3.3 Half-life

The plasma half-lives of unchanged budesonide, epimer 22R and epimer 22S were 2.8, 2.66 and 2.71 hours, respectively, following intravenous administration of ^{3}H-budesonide 500μg to 6 healthy volunteers (Ryrfeldt et al., 1982, 1984). Following inhalation, the plasma half-life of unchanged budesonide was 2.0 hours, which is similar to that found after intravenous administration (Ryrfeldt et al., 1982).

3. Therapeutic Trials in Asthma

Inhaled corticosteroids are now well established in the management of asthma in steroid-dependent patients, with the great majority of published work and clinical experience being derived from using beclomethasone dipropionate. The efficacy and safety of this agent has been consistently reported in both short and long term trials (for recent reviews see Brogden, 1983a,b; Brogden et al., 1984), and it has become the standard against which the efficacy of other inhaled corticosteroids are assessed. Consequently, it is not surprising that a high proportion of published therapeutic trials involving budesonide have been short term comparisons (usually of open crossover design) with beclomethasone dipropionate in patients with asthma of varying degrees of severity (section 3.3). Most of the remainder of the clinical trials have been short term crossover studies usually evaluating the effects of different doses or different dosing regimens of inhaled budesonide in adult asthmatics. However, some were placebo controlled (Baran, 1984; Henriksen, 1984; Henriksen and Dahl, 1983; Johansson and Dahl, 1984; Rosenhall et al., 1982b), others were only in children with asthma (Baran, 1984; Field et al., 1982; Henriksen, 1984; Henriksen and Dahl, 1983; Kjellman et al., 1982), and a small number were of medium to long term duration (Ädelroth et al., 1984; Laursen et al., 1983; Rosenhall et al., 1982a). Some of the trials have been presented as short reports or in letter form, which has complicated their evaluation because of the lack of essential information concerning patients, trial design, methods, and so forth (Dahl and Johansson, 1982a; Kjellman et al., 1982; Laursen et al., 1983; Stiksa et al., 1982; Toogood, 1983).

Considering that inhaled corticosteroids are intended for the longer term prophylaxis of asthma rather than the treatment of acute exacerbations, there seems to be an undue preponderance of studies of between 2 and 4 weeks duration (2 weeks being by far the most frequent duration of assessment for each active regimen or any given particular dose). Only a limited number of trials have been reported in which budesonide was administered for prolonged periods (section 3.2). While these studies showed a convincing steroid-sparing effect in patients with severe asthma, the relative efficacy of budesonide compared with other inhaled corticosteroids has not been assessed in long term studies.

3.1 Short Term Studies in Asthma

Even after single doses, inhaled budesonide produces a rapid improvement in pulmonary function characterised by a dose-response increase in peak expiratory flow rate (section 1.6). Following multiple doses (25, 100 or 400μg 4 times a day) in an appropriately designed 2-week crossover study in 18 patients with moderately severe asthma, dose-dependent increases in morning and evening peak

expiratory flow rates were also recorded (Johansson and Dahl, 1984) [fig. 7].

In this study there was a high drop-out rate during the placebo period which suggests that all 3 doses of budesonide were more effective than placebo, although 2 patients also withdrew while receiving the lowest dose of budesonide. Assessment of subjective scores for asthma severity revealed that budesonide 400 and 1600 μg/day was superior to 100 μg/day, but only a daily dose of 400μg was statistically different from placebo.

3.1.1 Inhaled Budesonide Compared with Oral Steroids

In severe steroid-dependent asthmatics, long term therapy with high dose oral steroids produces an increased incidence of side effects (Cochrane, 1983). Because of this, any oral steroid-sparing manoeuvre should be considered if disease stability can be maintained: a number of studies have attempted to compare the antiasthmatic efficacy of inhaled budesonide with that of oral prednisone.

In an open randomised 2-week crossover study in 16 patients with steroid-dependent severe asthma, daily doses of 400 and 800μg of inhaled budesonide appeared to be of equivalent potency as 10 and 20mg of oral prednisolone, as assessed by changes in peak expiratory flow rate and severity of asthmatic symptoms (Rosenhall et al., 1982b). In a double-blind crossover study, 14 prednisone-dependent patients and 17 patients not requiring oral steroid received 3 dosages of inhaled budesonide (400 to 3200 μg/day) and 3 dosages of alternate-day oral prednisone (7.5 to 60mg) for 2 weeks each (unpublished data on file, Astra; Toogood et al., 1983). After a stable baseline period (maintained with inhaled beclomethasone dipropionate with or without alternate-day oral steroid), it was impossible to adequately control asthmatic symptoms with alternate-day oral prednisone alone in prednisone-dependent patients. In contrast, budesonide alone, inhaled with the aid of a spacer, significantly improved asthma control, the best response being obtained with 800 to 1600 μg/day. In both prednisone-dependent patients and those not dependent upon oral prednisone, inhaled budesonide was superior to alternate-day oral prednisone in controlling asthma, as assessed by forced expiratory volume, severity of symptoms and attack frequency.

Comparable findings have been reported in 34 patients with severe unstable asthma requiring high doses of oral prednisone on alternate days (Toogood et al., 1984d). Patients received both inhaled budesonide (400 to 3200 μg/day in 4 divided doses) and oral prednisone (7.5 to 40mg once daily) for 6 weeks each, the actual dose being dependent upon the prior severity of the underlying disease. In a double-blind crossover trial, relapses of asthma were linearly related to the log dose of both drugs but the number of exacerbations requiring extra oral steroid occurred twice as often with oral prednisone ($p < 0.05$) and the relative potency for preventing severe relapses was 25 : 1 in favour of inhaled budesonide. The results of this study indicate that both inhaled budesonide and oral prednisone can effectively control unstable asthma providing that sufficiently large doses are used. However, at doses producing equivalent control of the asthmatic condition, inhaled budesonide had significantly less systemic activity, as measured by morn-

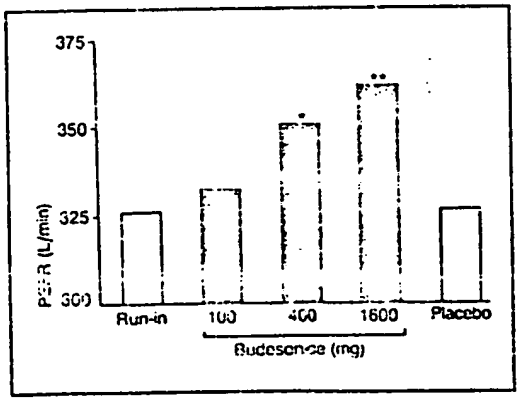

Fig. 7. Mean evening peak expiratory flow rates after ≥ 1 week run-in period (on inhaled beclometnasone dipropionate 400 μg/day), three 2-week treatment periods with different doses of inhaled budesonide (100, 400, and 1600 μg/day in 4 divided doses) and a 2-week placebo-controlled washout period in 18 patients with moderately severe asthma: * $p < 0.05$, ** $p < 0.01$ compared with placebo (after Johansson and Dahl, 1984).

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Similarly, in a placebo-controlled study, both inhaled budesonide 200 and 800 μg/day and inhaled beclomethasone dipropionate 400 μg/day produced greater increases in peak expiratory flow rates than 30 mg/day of oral prednisolone in 23 severely asthmatic patients maintained on a mixture of drugs, including minimum maintenance doses of oral corticosteroids (Rosenhall et al., 1982b). However, interpretation of these data is difficult due to a number of faults in the trial design and the difference in treatment duration – 1 week for prednisolone and 2 weeks for each inhaled dosage.

3.1.2 *Budesonide in Asthmatic Children*

Several short term therapeutic trials have evaluated the clinical efficacy of inhaled budesonide in children with asthma. Some of these were direct comparisons with beclomethasone dipropionate (see section 3.3), which indicated that the 2 drugs were of approximately equal potency (Field et al., 1982; Kjellman et al., 1982). However, in a recent double-blind crossover trial in 21 asthmatic children, budesonide 100μg twice daily inhaled with a spacer was found to produce significantly greater improvements in morning and evening peak expiratory flow rates and in forced expiratory volume than equal doses of beclomethasone dipropionate inhaled with a standard actuator (Baran, 1984). Another double-blind placebo-controlled study investigated the effect of single doses of inhaled terbutaline (32.5μg) on lung function in 14 children with exercise-induced asthma before and during 4 weeks' treatment with inhaled budesonide (400 μg/day through a 750ml cone spacer) [Henriksen and Dahl, 1983]. The main aim of the trial was to assess whether sustained therapy with budesonide could possibly potentiate the effects of terbutaline; the results support the view that the interaction between the 2 drugs was probably additive. At rest, 1 week's treatment with budesonide produced a significant improvement in lung function, as assessed by changes in peak expiratory flow rate, forced expiratory volume in one second and forced expiratory flow in the middle half of forced vital capacity, and there was a further small improvement by week 4. The bronchoconstrictor response to exercise was reduced following 4 weeks' treatment with budesonide and this mirrors the findings obtained with other inhaled corticosteroids – single doses of which did not inhibit exercise-induced asthma but therapy for 2 to 4 weeks did afford some protection (Hartley et al., 1977; Hodgson et al., 1974). As a follow-up to this trial the effectiveness of inhaled budesonide (400 μg/day with a spacer) in preventing exercise-induced asthma was evaluated in a 3-week double-blind placebo-controlled crossover study in 16 asthmatic children (Henriksen, 1984). Of 14 children who completed the trial, 12 gained significant protection from exercise-induced asthma while receiving budesonide and the mean fall in forced expiratory volume after exercise was reduced by 63%.

3.1.3 *Twice Daily vs Four Times Daily Administration*

Experience with beclomethasone dipropionate indicates that moderate asthma can be well controlled with a twice or 4 times daily dosing schedule when the asthma is stable (Brogden et al., 1980). Since poor compliance has been implicated as a possible factor in reducing the efficacy of inhaled corticosteroids, any reduction from the conventional 4-times-a-day regimen may help improve compliance and consequently the efficacy of inhaled steroids.

In a number of studies, budesonide inhaled twice daily has proved to be as effective as beclomethasone dipropionate inhaled 4 times a day in patients with chronic asthma (Willey et al., 1982), steroid-dependent severe asthma (Stiksa et al., 1982), and in children with severe asthma (Field et al., 1982). When budesonide (800 μg/day) was administered

both twice and 4 times daily, no reduction in therapeutic efficacy was observed as a result of reducing the dose frequency (Stiksa et al., 1982). These findings were supported by the results of a recent study in which twice and 4 times daily administration of budesonide (400 μg/day with a spacer) were compared in a double-blind 4-week crossover trial in 19 patients with stable asthma not requiring oral steroids (Nyholm et al., 1984). Assessment of pulmonary function (peak expiratory flow rate, forced expiratory volume and forced vital capacity) and asthma symptoms indicated that twice daily treatment with budesonide was at least as effective as a 4 times daily regimen. However, in a comprehensive study specifically designed to evaluate the influence of various dosing regimens on the response of 34 severely asthmatic patients to aerosol budesonide, daily doses of 400, 800 and 1600μg were administered 2 or 4 times a day for 2 weeks each in a crossover trial (Toogood et al., 1982a,b). At every dose level of budesonide the best results (regardless of index measured) were consistently observed with the 4 times daily dose regimen, in agreement with these results are the findings of Dahl and Johansson (1982a) who showed that a reduction in dose frequency from 4 times daily to twice daily in 16 patients with moderately severe asthma produced a significant decrease in evening peak expiratory flow rate, although the morning rate was unchanged. The apparently contradictory conclusions drawn from these trials may reflect differences in the activity of the asthmatic state of the patients studied. Whether the small (but statistically significant) improvements in lung function in favour of the more frequent dosing regimens found in some short term studies do indeed afford greater antiasthmatic protection against periods of acute exacerbation remains uncertain. However, until this matter is clarified it may be clinically prudent, especially for patients in relapse where a more frequent budesonide regimen has been shown to be significantly superior, to employ a 4-times-a-day dosing schedule.

3.1.4 Effect of Spacer Devices

In a number of trials budesonide has been administered with an extension or spacing (spacer) device (for examples see table II). This could be an important consideration when evaluating such studies since it has been shown that these devices can increase drug deposition in the lung and decrease unwanted deposition in the oropharynx (Newman et al., 1981). In the study of Björkander et al. (1982) it was shown that budesonide 50μg 4 times daily inhaled through a spacer was slightly more efficacious, with respect to reducing the need for supplemental β$_2$-agonists and in relieving symptoms, than an equivalent dose of budesonide or beclomethasone 100μg 4 times daily, both administered with a standard actuator. However, each treatment period was only 2 weeks in duration and changes in peak expiratory flow were not significantly different.

In studies designed to specifically evaluate the influence of an 80ml tube spacer, a 750ml cone spacer, and a conventional actuator for administering low (400 μg/day) and high (1600 μg/day) doses of budesonide to 35 asthmatics it was found that both spacers may be clinically useful in that they augment the airway response to budesonide and reduce the level of oropharyngeal candidiasis (section 6.1.1) (Toogood et al., 1984b,c). The 2 spacers doubled the antiasthmatic potency of inhaled budesonide as assessed by the change in forced expiratory volume in 1 second from baseline ($p < 0.05$), and this occurred despite preselecting and pretraining this group of patients to achieve maximum efficiency using a standard actuator. The results from this study indicate that all asthmatic patients receiving budesonide deserve a trial with a spacer, since approximately 90% of them may be expected to show an improvement in asthma control and/or reduced oropharyngeal complications, and at present there is no accurate method of predicting those likely to respond (Toogood et al., 1984c).

3.2 Long Term Studies in Asthma

Long term trials with inhaled budesonide have all been of open design in patients with severe asthma; assessments were made to evaluate changes

in lung function and symptomatology, and the need for oral steroids and hospitalisation (for acute exacerbations). In the largest study to date, 166 adult asthmatics dependent upon inhaled steroids entered an 8-centre trial designed to investigate the safety and efficacy of budesonide 100μg 4 times daily inhaled via a spacer (unpublished trial, Astra). 134 patients completed 1 year of treatment and of the 32 withdrawals only 10 were due to adverse effects: 14 were due to other medical reasons (such as deterioration or improvement of the underlying disease) and 8 were for non-medical reasons. During the trial the number of patients requiring supplemental oral steroids decreased, although conclusions with respect to this should be guarded since only a small percentage (18.7%) of patients required oral steroids at entry. Lung function, as assessed by forced expiratory volume, significantly improved during the 12-month treatment period, but there was no change in forced vital capacity. In addition, bronchodilator-induced increases in forced expiratory volume and vital capacity were significantly reduced during follow-up, compared with the bronchodilator-induced increases at baseline. In parallel with the improvement in lung function, daytime and night-time symptom scores for wheeze, breathlessness, tightness of the chest, cough and sputum were all significantly reduced throughout follow-up, and the respiratory rate was also significantly decreased. 77 patients continued for a second year (only 4 centres participated) and the results did not appear to show any new effects or changes compared with the first year, although firm conclusions await separate statistical analysis for this subgroup.

All other long term trials have been in patients dependent upon oral prednisone and have primarily assessed the possibility of reducing the requirement for oral steroid during high dose therapy with inhaled budesonide. Thus, in 31 prednisolone-dependent asthmatics (mean duration 12.3 years) who were treated with inhaled budesonide (mean dose 1060 μg/day) for 12 months, the mean daily consumption of oral steroid was reduced from 9 to 2.5mg (Rosenhall et al., 1982a). During the trial, mean peak expiratory flow rate increased from 250 to 320 L/min in the morning and from 320 to 360 L/min in the evening, with those patients who had the highest prednisolone intake at the start of the study gaining the most benefit. Additionally, there was a marked reduction in the number of exacerbations of asthma per month and a gradual increase in plasma cortisol concentrations *(see section 1.3)*. As a continuation of this trial, 38 patients with chronic asthma requiring continuous oral corticosteroids (87% required 5 to 15mg of prednisolone each day and the remainder were on alternate-day therapy) were followed for 2 years, and during this period budesonide (inhaled via a tube spacer) was carefully substituted for the oral ster-

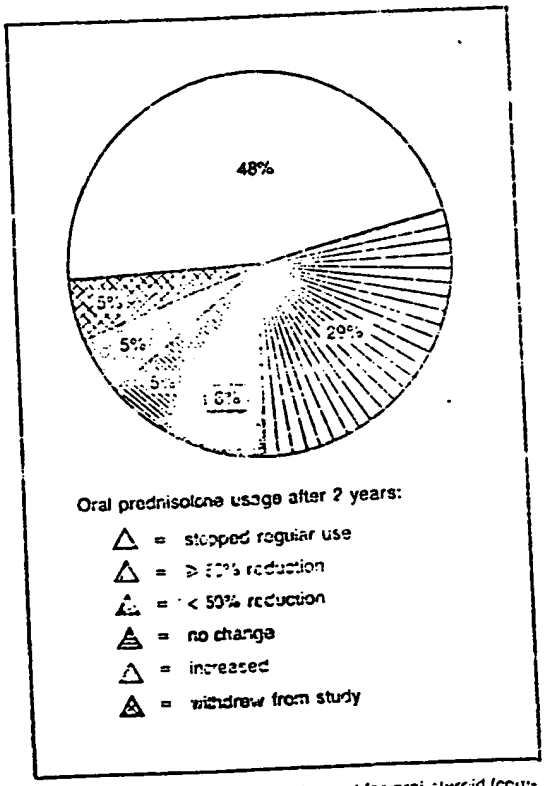

Fig. 3. Summary of patients' requirement for oral steroid (compared with baseline) after 2 years' therapy with high dose inhaled budesonide (800 to 1600 μg/day) in an open study of 38 patients with steroid-dependent severe asthma (after Agertoft et al., 1984).

oid (Ädelroth et al., 1984). At the end of 2 years the majority of patients were able to stop the use of, or greatly reduce (≥ 50%) the need for, oral prednisolone (fig. 8). Comparing the second year of the trial with the year preceding it, hospital admissions and the number of days of treatment caused by acute attacks of severe asthma were reduced by 73% and 76%, respectively. During the study, half the reduction of oral steroid was achieved in the first 3 months and was almost completed within 6 months. At the same time, morning and evening peak expiratory flow rates considerably increased and total symptom scores reduced by approximately 33%.

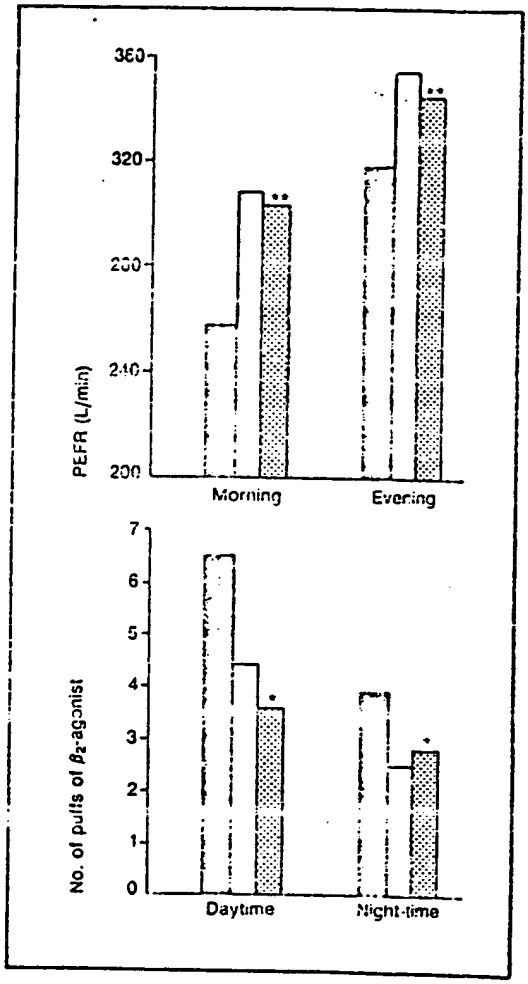

Fig. 9. Mean values of peak expiratory flow rate (PEFR) and supplemental β_2-agonist usage during 14-day assessment periods, before (▨) and during high dose prednisone treatment (□) and after 6 months' therapy with budesonide 1600 μg/day (▩) in a 6-month prospective study in 49 patients with severe asthma: * $p < 0.05$; ** $p < 0.001$ compared with corresponding values before treatment (after Laursen et al., 1983).

Findings of a similar nature were observed in a prospective 6-month controlled trial in 49 steroid-dependent (prednisone 10 to 40mg daily) severe asthmatics whose mean disease duration was 18 years (Laursen et al., 1983). Before initiating therapy with aerosol budesonide 800μg twice daily with a spacer, each patient underwent 7 days' treatment with prednisone 40mg to establish near maximal bronchodilation. By the end of the study oral prednisone intake was reduced from 13.9 to 6.0 mg/day and lung function, as assessed by peak expiratory flow rate, was greatly improved (20% in the morning and 10% in the evening); there was also a concomitant significant reduction in the requirement for supplemental β_2-agonist inhalations (fig. 9).

The lack of placebo controls in all of these trials might have masked any tendency for spontaneous improvement in asthmatic status that can occasionally occur, but this seems unlikely considering the severity of the underlying disease. The striking improvements observed are encouraging but further long term studies are needed to clearly establish the place of inhaled budesonide in the treatment of asthma compared with other available inhaled corticosteroids.

3.3 Budesonide Compared with Other Inhaled Corticosteroids

Beclomethasone dipropionate is the most widely studied inhaled steroid available for the treatment of asthma, and it is the standard by which newer inhaled steroids are compared. It is therefore not surprising that all the comparative studies involving budesonide have been with beclomethasone dipropionate (table II). In design, a small number of

Table II. Summary of design and results of short term therapeutic trials comparing aerosol budesonide (BUD) and beclomethasone dipropionate (BDP) in the treatment of asthma

Reference	No. of patients[a]	Diagnosis	Study design	Duration of therapy[b] (weeks)	Daily dosage (mg/day)		Assessment criteria	Overall results[c]
					BUD	BDP		

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Table II. Summary of design and results of short term therapeutic trials comparing aerosol budesonide (BUD) and beclomethasone dipropionate (BDP) in the treatment of asthma

Reference	No. of patients[a]	Diagnosis	Study design	Duration of therapy[b] (weeks)	Daily dosage (frequency)		Assessment criteria	Overall results[c]
					BUD	BDP		
Baran (1984)	21	Children with chronic asthma	r, db, co, pc	3	200μg (bid)[d]	200μg (bid)	PEF, FEV_1, VC, and diary cards	BUD > BDP
Bjorkander et al. (1982)	12	sd, stable, moderate asthma	r, co, pc	2	400μg (qid)	400μg (qid)	PEF, FEV_1, VC and diary cards	BUD = BDP
Bjorkander et al (1982)	23	sd, stable, moderate asthma	r, co, pc	2	200μg (qid)[d]	400μg (qid)	PEF, FEV_1, VC and diary cards	BUD = BDP
Field et al. (1982)	27	Children with severe asthma	r, db, co	4	400μg (bid)[e]	400μg (qid)	PEF, FEV_1, VC and diary cards	BUD > BDP
Kjellman et al. (1982)	16	Children with severe, sd asthma	r, open, co	3	full dose (bid)[e] half dose (bid)[e]	full dose (bid) full dose (bid	PEF and symptom scores	BUD = BDP BUD = BDP
Rosenhall et al. (1982b)	23	sd, severe asthma	r, open, co	2	200μg (qid) 800μg (tid)	400μg (qid)	PEF, FEV_1, VC and diary cards	BUD = BDP
Stiksa et al. (1982)	27	sd, severe asthma	r, open, co	2	800μg (qid) 800μg (bid)	800μg (qid) 800μg (qid)	PEF and diary cards	BUD = BDP BUD = BDP
Wiley et al. (1982)	30	nsd, chronic asthma	r, db, co	4	400μg (bid)[e]	400μg (qid)	PEF, FEV_1, VC and diary cards	BUD = BDP

a Number of patients who completed the trial.
b Duration of treatment with each active regimen.
c BUD = BDP signifies that the 2 drugs produce equivalent changes; BUD ≥ BDP indicates a trend in favour of budesonide; BUD > BDP indicates that budesonide was significantly better than beclomethasone dipropionate.
d Administered with and without a spacer.
e Administered with a spacer.

Abbreviations: db = double blind; co = cross over; r = randomised; pc = placebo-controlled; sd = steroid-dependent; nsd = non-steroid-dependent; bid = twice daily; qid = 4 times daily; PEF = peak expiratory flow rate; FEV_1 = forced expiratory volume in one second; VC = vital capacity.

the trials were double-blind (Baran, 1984; Field et al., 1982; Willey et al., 1982); the remainder were non-blind - all were randomised crossover comparisons in patients with asthma of reasonably well-defined severity. The duration of treatment was short term (between 2 and 4 weeks) in every study and, since there is a strong carryover of antiasthmatic effects with inhaled corticosteroids, it would seem unlikely that trials of such short duration could detect small therapeutic differences in 2 drugs of similar activity.

Drug-induced changes in asthmatic status were assessed by peak expiratory flow rate and symptom scores in every study, and also by changes in forced expiratory volume in one second and vital capacity in most other trials (see table II). The majority of studies show that with short term use inhaled budesonide and inhaled beclomethasone dipropionate are of approximately equal efficacy in children with asthma (Field et al., 1982; Kjellman et al., 1982), in steroid-dependent asthmatics (Björkander et al., 1982; Rosenhall et al., 1982b; Stiksa et al., 1982) and in patients not dependent upon oral prednisolone (Willey et al., 1982). The only trial to find any significant differences between these 2 inhaled corticosteroids was the study of Baran (1984): budesonide administered with a spacer to asthmatic children was significantly superior to beclomethasone dipropionate (see section 3.1.2). However, the different methods of administering the 2 drugs makes it difficult to interpret the findings in terms dose equivalency. The relative efficacy of budesonide and beclomethasone dipropionate following long term administration has not been reported.

4. Therapeutic Trials in Rhinitis

The therapeutic efficacy of intranasal budesonide has been evaluated in patients with seasonal allergic, perennial allergic and perennial non-allergic (vasomotor) rhinitis in open, single-blind and double-blind trials. In the majority of studies comparisons were made with placebo although there have also been a number of comparisons with other active treatments. These include single-blind comparisons with beclomethasone dipropionate (Pipkorn, 1983b; Pipkorn and Runderantz, 1982; Samuelsson, 1983), a single-blind comparison with flunisolide (Pipkorn and Geterud, 1984), a single- and a double-blind comparison with sodium cromoglycate (unpublished trial on file, Astra) and a double-blind comparison with the antihistamine dexchlorpheniramine (Munch et al., 1983).

Since there is no proven and reliable technique for measuring the severity of symptoms associated with rhinitis, subjective assessment of changes in disease status, as recorded on patient symptom diary cards, has been the most extensively used method. Recently, rhinomanometry has been used to determine nasal airway resistance in patients with non-allergic perennial rhinitis (Malm et al., 1981) and in children with perennial allergic rhinitis associated with bronchial asthma (Wenzel et al., 1983), although in the former study the results did not correspond with nasal symptom scores or nasal secretion following methacholine challenge.

4.1 Comparisons with Placebo in Seasonal Allergic Rhinitis

Due to the seasonal nature of the disease and because spontaneous variation in atmospheric allergen levels occur, it is desirable that therapeutic trials in patients with seasonal allergic rhinitis should be placebo-controlled. It is also essential that pollen counts are recorded to indicate the severity of exposure. Several short term placebo-controlled double-blind comparisons in parallel groups of patients have been reported with budesonide (Cameron et al., 1984; Norman et al., 1984; Pipkorn et al., 1980; Steensen and Lindqvist, 1981; Warland et al., 1981) [table III]. Most of these trials were performed in Scandinavia (Denmark, Norway and Sweden) although one was carried out in a general practice setting in England (Cameron et al., 1984) and one was carried out in the United States (Norman et al., 1984).

The results from these trials have shown intranasal budesonide 400 μg/day to be significantly more effective than placebo in relieving nasal symptoms (blockage, discharge and sneezing) and

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Table III. Summary of the design and results of studies comparing budesonide (BUD) administered twice daily with placebo (P) in patients with seasonal or perennial rhinitis

Reference	No. of patients[a]	Study design	Daily dosage (μg)	Duration of therapy (weeks)	Results[b]			
					nasal symptom score	eye symptom score	supplementary antiallergy drugs	nasal airway resistance
Seasonal rhinitis								
Cameron et al. (1984)	60	db, pg	400	4	BUD > P	BUD < P	BUD > P	
Norman et al. (1984)	50	db, pg	400	4	BUD > P			
Pipkorn et al. (1980)	36	db, pg	400	3	BUD > P		BUD > P	
Steensen and Lindqvist (1981)	39	db, pg	200 400	2	BUD > P	BUD ≡ P	BUD > P	
Warland et al. (1981)	29	db, pg	400	3	BUD > P		BUD > P	
Perennial rhinitis								
Batra et al. (1980)[c]	26	db, co	200 400	2	BUD > P			
Henriksen and Wenzel (1983)[d]	35	db, pg	400	4	BUD > P			
Holopainen et al. (1982)[e,f]	19	db, pg	400	16	BUD > P			
Malm et al. (1981)[d]	22	db, co	50, 200 and 800	2	BUD > P			BUD ≡ P
Wenzel et al. (1983)[d]	37	db, pg	400	4				BUD > P

a Number of patients who completed the trial.
b BUD > P signifies that budesonide produced a significantly more favourable response than placebo; BUD ≡ P indicates that budesonide and placebo produced equivalent changes; BUD < P signifies that placebo produced a significantly better response.
c Children with bronchial asthma and perennial allergic rhinitis.
d Patients with perennial non-allergic rhinitis.
e Patients with allergic or non-allergic rhinitis.
f Patients with nasal polyps.
Abbreviations: db = double-blind; co = crossover; pg = parallel groups of patients used.

in reducing the need for supplemental antiallergy tablets. In one of these trials (Steensen and Lindqvist, 1981) budesonide 200 μg/day was effective in alleviating nasal symptoms, but this study was performed in a season when pollen counts were low; whether this dosage regimen would be equally effective during periods of high exposure remains to be verified. Budesonide was found to have no effect on the severity of eye symptoms. Indeed, in the study of Cameron et al. (1984), patients receiving intranasal budesonide 400 μg/day had significantly more severe eye symptoms than did a placebo group, although they did not resort to using more eye drops to relieve these symptoms. In contrast, in the trial of Steensen and Lindqvist (1981) patients in the budesonide group did use more eye drops to alleviate eye symptoms than did a placebo group, and consequently no significant change in total eye symptoms could be demonstrated between the groups. A similar lack of effect on eye symptoms has been observed when using intranasal beclomethasone dipropionate in patients

with seasonal allergic rhinitis (Brogden et al., 1984).

In a study of 50 grass-allergic patients characterised by spring hayfever, symptom scores were significantly reduced ($p = 0.001$) by intranasal budesonide compared with placebo (Norman et al., 1984). Mediator analysis from nasal washes revealed that histamine content was not significantly altered by treatment, whereas the concentration of another allergic mediator [tosyl-arginine methyl ester (TAME)-esterase] was significantly lowered by budesonide (3594 to 1759 counts/min) but not by placebo (3019 to 3385 counts/min).

4.2 Trials in Perennial Rhinitis

Perennial vasomotor rhinitis is a common and frequently very uncomfortable condition that is characterised by non-seasonal sneezing, nasal discharge, and nasal congestion. It is normally termed 'allergic' when a specific allergen is considered responsible and 'vasomotor' when no such allergic component can be identified (Balle et al., 1980). Intranasal budesonide has been used in the treatment of allergic and non-allergic perennial rhinitis. Both double-blind comparisons with placebo (table III) and long term open trials have been published (Balle, 1982; Lindqvist et al., 1982, 1983; Pipkorn and Berge, 1983), but the failure in some of these studies to clearly distinguish between allergic and non-allergic patients makes interpretation of the results difficult in such cases.

4.2.1 Placebo-Controlled Studies

Placebo-controlled double-blind comparisons have shown intranasal budesonide to be superior to placebo in patients with perennial non-allergic rhinitis (Malm et al., 1981), perennial allergic or non-allergic rhinitis (Balle et al., 1980), perennial non-allergic rhinitis with small nasal polyps (Holopainen et al., 1982), and in children with perennial allergic rhinitis associated with bronchial asthma (Henriksen and Wenzel, 1983; Wenzel et al., 1983). Generally daily doses of 200 or 400 µg have proved effective although a dose of 50 µg/day was also found to significantly relieve nasal symptoms (without significantly reducing methacholine-induced secretions) in patients with non-allergic rhinitis (Malm et al., 1981). In this study budesonide was administered intranasally at 3 dosages – 50, 200 and 800 µg/day – but no clear dose-response relationship was observed and there was no statistically significant difference between any of the 3 dosages and placebo, with respect to changes in nasal airway resistance measured rhinomanometrically. In contrast, approximately half the patients had nasal eosinophilia before treatment and this was significantly reduced by budesonide so that after the last treatment period only 2 patients had nasal eosinophilia. A similar finding was observed in patients with perennial rhinitis with associated nasal polyposis, in whom intranasal budesonide caused a pronounced reduction in tissue eosinophilia (Holopainen et al., 1982). A previous placebo-controlled double-blind trial noted budesonide was effective in patients with vasomotor and allergic rhinitis, but when they were subdivided regarding nasal eosinophilia, budesonide was only effective in those with eosinophilia (Balle et al., 1980).

4.2.2 Open Studies

Budesonide has been used in several long term open trials in patients with perennial rhinitis, but in one of these (Balle, 1982) only adverse reactions to treatment were reported in 15 patients treated for up to 30 months (see section 6.2). In a recently reported study (Pipkorn and Berge, 1983), 12 patients with vasomotor rhinitis received intranasal budesonide for 1 year. Initial dosage was 400 µg/day and symptoms were consistently relieved throughout the study period and no symptom relapse was observed; at the end of the trial 3 patients had reduced their daily dosage to 200µg and no dosage increases were required. A 6-month open study in 86 patients with perennial rhinitis (in 38 it was classified as allergic) showed that intranasal budesonide 200 to 400 µg/day significantly reduced severity of all nasal symptoms after 3 and 6 months of therapy (Lindqvist et al., 1982). Similarly, in a 12-month open study in 106 adults with perennial rhinitis, intranasal budesonide (200 to 400 µg/day) produced a significant decrease in all nasal symptoms (Lindqvist et al., 1983).

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The conclusions from all these long term studies have been that intranasal budesonide is safe and effective in the treatment of perennial rhinitis. However, the open nature of these trials and the absence of long term comparative studies (see section 4.3) prevent a clear conclusion as to the relative efficacy of intranasal budesonide compared with other intranasal steroids in perennial rhinitis.

4.3 Budesonide Compared with Other Drugs

To date, there have been no studies comparing budesonide with other drugs in patients with perennial (allergic or non-allergic) rhinitis. However, several studies have been reported comparing intranasal budesonide with alternative active treatments in patients with seasonal allergic rhinitis (table IV). In these trials intranasal budesonide was found to be as effective as intranasal flunisolide (Pipkorn and Geterud, 1984), more effective than intranasal sodium cromoglycate (unpublished trials on file, Astra) and the oral antihistamine dexchlorpheniramine maleate (Munch et al., 1983), and at least as effective as intranasal beclomethasone dipropionate (Pipkorn, 1983b; Pipkorn and Rundcrantz, 1982; Samuelsson, 1983). Generally, each trial was well-designed (single- or double-blind randomised comparisons in parallel groups of patients) with a 1-week run-in period followed by 3 weeks' active treatment, but little or no information regarding group comparability was presented.

In 91 patients sensitive to either birch or grass pollen, budesonide 200μg twice daily was significantly more effective in relieving nasal symptoms than beclomethasone dipropionate 100μg 4 times daily during the months of May and June, when pollen counts revealed high levels of birch and grass pollen, respectively (Pipkorn and Rundcrantz, 1982) (fig. 10). Both in this study and in the more recent trial of Samuelsson (1983) it was concluded that differences between budesonide and beclomethasone dipropionate were more easily detected when pollen counts were high. In the only other comparison between these 2 agents, both seemed equally effective when administered twice daily, although the pollen levels during this trial were ex-

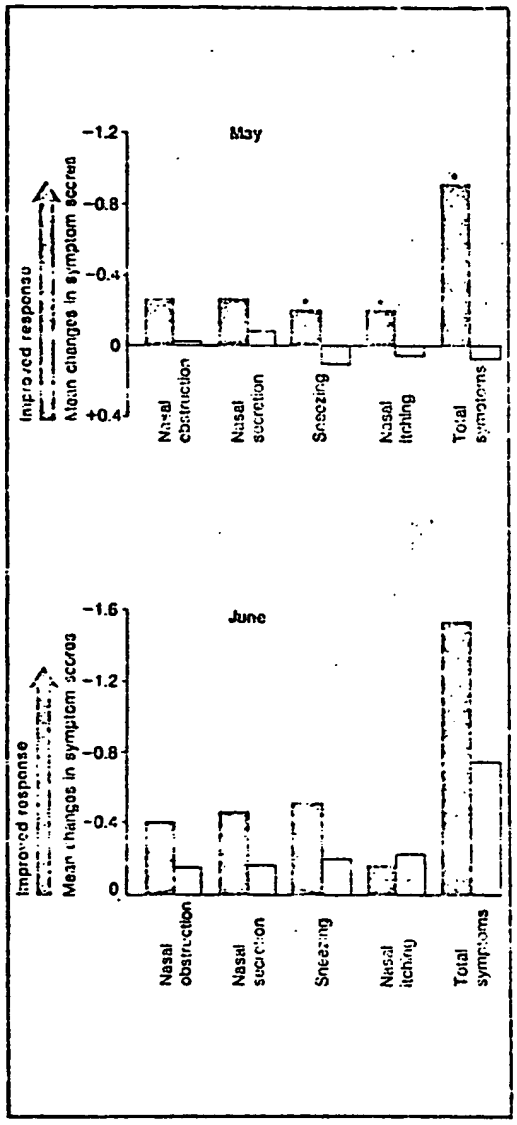

Fig. 10. Comparison between the effects of intranasal budesonide (200μg twice daily (▨)) and intranasal beclomethasone dipropionate (100μg 4 times daily (□)) on the mean symptom scores relative to baseline values, in 91 patients with seasonal allergic rhinitis. 64 patients were treated in May (31 with budesonide) and 27 in June (15 with budesonide) when there were high levels of birch pollen and grass pollen, respectively; * significant difference between treatments (after Pipkorn and Rundcrantz, 1982).

Table IV. Summary of randomised short term (3-week) therapeutic trials in parallel groups of patients with seasonal allergic rhinitis comparing intranasal budesonide (200µg bid) with alternative active treatments

Reference	No. of patients (budesonide group)[a]	Allergen (diagnosis)	Study design	Dosage of alternative therapy (route)	Results[b]					
					total nasal symptoms	nasal blockage	nasal sneezing	nasal itching	eye symptoms	patient preference
Comparison with dexchlorpheniramine maleate										
Munch et al. (1983)	60 (31)	Birch pollen (history, st)	db	6mg bid (po)	BUD > DCP	BUD > DCP	BUD > DCP	BUD ≥ DCP	BUD = DCP[c]	BUD ≥ DCP
Comparison with flunisolide										
Pipkorn and Caterud (1984)	58 (30)	Birch pollen (history, st)[d]	sb	100µg bid (in)	BUD = F	BUD = F	BUD = F		BUD = F	BUD ≥ F
Comparisons with beclomethasone dipropionate										
Pipkorn (1983b)	51 (26)	Birch pollen (history, st)	db	200µg bid (in)	BUD = BDP	BUD = BDP	BUD > BDP	BUD = BDP	BUD = BDP	
Pipkorn and Runderantz (1982)	64 (31)	Birch pollen (history, st)	sb	100µg qid (in)	BUD > BDP	BUD ≥ BDP	BUD > BDP	BUD > BDP		BUD > BDP
	27 (15)	Grass pollen (history, st)	sb	100µg qid (in)	BUD ≥ BDP	BUD ≥ BDP	BUD ≥ BDP	BUD = BDP		BUD > BDP
Samuelsson (1983)[e]	41 (nd)	Birch pollen (verified)[f]	sb	200µg bid (in)		BUD > BDP				
Comparisons with sodium cromoglycate										
Unpublished trial	42 (21)	Grass pollen (history, st)	db	5.2mg 6× daily (in)	BUD > SCG	BUD > SCG	BUD > SCG	BUD > SCG	BUD > SCG	BUD > SCG
Unpublished trial[g]	42 (21)	Birch pollen (history, st, npt)	sb	5.2mg 6× daily (in)	BUD > SCG	BUD > SCG	BUD > SCG	BUD > SCG	BUD = SCG	BUD ≥ SCG

a Number of patients who completed the trial.
b BUD > signifies budesonide was significantly better; BUD ≥ signifies a trend in favour of budesonide; BUD = signifies that the 2 drugs produced equivalent results.
c Budesonide group used significantly more antihistamine + vasoconstrictor eye drops.
d Diagnosis was made by nasal provocation testing in 1 patient.
e Presented as a brief abstract with few details.
f Method of verification not stated.
g Treatment period in this study was 4 weeks.

Abbreviations: BUD = budesonide; DCP = dexchlorpheniramine maleate; F = flunisolide; BDP = beclomethasone dipropionate; SCG = sodium cromoglycate; db = double-blind; sb = single-blind; st = skin tests; npt = nasal provocation tests; po = oral; in = intranasal; bid = twice daily; qid = 4 times daily; nd = no details of group sizes.

tremely low – approximately 15 times less than the previous season.

Pollen levels were quite high when intranasal budesonide and intranasal flunisolide were compared and both drugs appeared equally efficacious (Pipkorn and Geierud, 1984). Similarly, during a 4-week comparison with intranasal sodium cromoglycate (5.2mg 6 times daily) birch pollen levels were high and intranasal budesonide 200μg twice daily was significantly better in reducing nasal symptoms (unpublished trial on file, Astra). In this study there was no significant difference between the 2 treatment groups with respect to the severity of eye symptoms. Pollen counts were not performed during another comparison between intranasal budesonide (200μg twice daily) and intranasal sodium cromoglycate (5.2mg 5 times daily), and all symptom scores (including eye symptoms) were significantly lower for the budesonide group (unpublished trial on file, Astra). Finally, due to bad weather, pollen counts were extremely low when intranasal budesonide was compared with oral dexchlorpheniramine and this may explain why for a number of nasal symptoms only trends in favour of the intranasal corticosteroid were observed and not statistically significant advantages (Munch et al., 1983). These results clearly show the need to qualify the severity of allergen exposure when comparing drugs in patients with seasonal allergic rhinitis.

5. Treatment of Nasal Polyposis

The therapeutic efficacy of intranasal budesonide (400 μg/day) administered from an aqueous nasal pump spray in nasal polyposis was compared with placebo in a double-blind parallel group 16-week study in 19 patients with perennial intrinsic nasal symptoms associated with small nasal polyps (Holopainen et al., 1982). Budesonide was significantly more effective than placebo in reducing total symptom scores and increasing nasal peak flow rates. In addition, rhinoscopy revealed a distinct decrease in nasal congestion, a decrease in polyp size and a significant reduction in the number of polyps, all without evidence of drying and crusting, for those patients treated with budesonide. While such findings are encouraging, since only 10 patients received active treatment in this study a larger controlled study is needed to clearly establish the place of budesonide in the treatment of nasal polyposis.

6. Side Effects

6.1 Inhaled Budesonide

In general terms, inhaled budesonide has been well-tolerated, with a high proportion of the published clinical trials to date reporting no adverse events associated with treatment. However, as previously emphasised (section 3), the majority of these studies in asthmatic patients have been of short term design (2 to 4 weeks) with only a small number of trials of greater than 4 weeks duration. Additional longer term clinical experience is needed to clearly establish the side effects profile of inhaled budesonide.

6.1.1 Candidiasis, Dysphonia and Sore Throat

The most commonly reported adverse effects associated with the administration of inhaled budesonide have been oral candidiasis, dysphonia (hoarseness) and sore throat, as occurs with other inhaled corticosteroids (Brogden, 1983c). The relative incidence of oral candidiasis has varied widely, with some studies not finding any fungal growth (Willey et al., 1982) nor any increase in growth compared with baseline levels when each patient was receiving oral steroid therapy (Rosenhall et al., 1982a), while another reported a dose-response relationship between the total daily dose of budesonide inhaled without a spacer and the number of *Candida* colonies counted (Toogood et al., 1984a). In this latter study, budesonide inhaled without a spacer on a twice daily basis, instead of 4 times daily, abolished the effect of increasing the daily dose of budesonide on candidiasis and almost eliminated the need for nystatin, but it was also associated with a small but significant deterioration of peak expiratory flow rate. The severity of dysphonia was also evaluated in this trial and was found to be infrequent at the start of the study and was unaffected by the daily dose or dose fre-

a Presented as a brief abstract with few details.
b Method of verification not stated.
c Treatment period in this study was 4 weeks.
Abbreviations: BUD = budesonide; DCP = dexchlorpheniramine maleate; F = flunisolide; BDP = beclomethasone dipropionate; SCG = sodium cromoglycate; db = double-blind; sb = single-blind; ST = skin tests; nat = nasal provocation tests; po = oral; in = intranasal; bid = twice daily; qid = 4 times daily; nd = no details of group sizes.

quency of inhaled budesonide. An earlier trial of comparable design revealed significantly less candidiasis when budesonide was inhaled with a spacer (80 or 750ml) compared with a conventional actuator, but there were no significant differences in the incidence of dysphonia among the 3 inhalers (Toogood et al., 1982c, 1984c). However, the level of dysphonia was minimal initially, so no firm conclusions should be drawn with respect to the effect of spacers on its relative incidence, although administration of beclomethasone dipropionate with a spacer has been shown to reduce dysphonia (Toogood et al., 1981). The changes observed for budesonide were independent of oral prednisone usage which has previously been implicated in increasing the risk of candidiasis when the drug is inhaled without a spacer.

6.1.2 Systemic Corticosteroid Withdrawal Effects

Of the long term trials published (section 3.2) only the studies of Ädelroth et al. (1984) and Rosenhall et al. (1982a) reported the incidence of adverse effects associated with high dose inhaled budesonide therapy. In the latter trial, 31 prednisolone-dependent asthmatics entered the study and inhaled budesonide was gradually substituted for the oral steroid. During the 1 year of follow-up, 11 patients had no adverse effects, 9 reported hoarseness or sore throat at least once (in 1 case it was severe enough to warrant withdrawal from the trial), 13 developed arthralgia or myalgia, 3 had exacerbation of eczema and 1 patient each developed pulmonary eosinophilia and sarcoidosis. In a continuation of this trial in 38 patients with chronic asthma, inhaled budesonide (200 to 1600 μg/day) was gradually substituted for oral prednisone and a similar level of adverse effects was recorded (Ädelroth et al., 1984). These side effects can all be explained in terms of a local reaction or the direct result of oral steroid withdrawal. This is similar to the findings with other inhaled corticosteroids where exacerbation of a previously controlled underlying disease has been reported following substitution of oral with inhaled steroid (Brogden, 1983c).

6.1.3 Adrenal Suppression

As noted previously (section 1.3), inhaled doses of budesonide (up to 800 μg/day) are not normally associated with significant reductions in plasma cortisol concentrations, and substitution of inhaled budesonide for oral prednisolone has generally resulted in a gradual improvement in plasma cortisol levels. However, in a recently reported 6-week trial in 28 chronic asthmatics who were poorly controlled with normal inhaled doses of beclomethasone dipropionate (mean 883 μg/day), high inhaled dosages of budesonide (1600 μg/day) or beclomethasone dipropionate (1500 μg/day) were of benefit to the majority of patients but they also caused some adrenal suppression (Ebden and Davies, 1984). This resulted in lower morning plasma cortisol levels compared with baseline values, but neither corticosteroid had any significant effect on the cortisol response to tetracosactrin stimulation. To date, the stimulatory response to tetracosactrin has been the most widely used test in both adult and child asthmatics receiving usual doses of budesonide, and no abnormal results have been noted (section 1.3). Since recovery of HPA function after long term oral corticosteroid therapy may take up to a year, it is essential to take special care during this period, if inhaled budesonide is to be substituted, so as to enable the patient to cope with stressful situations such as trauma, surgery, severe infections or an acute attack of asthma.

6.1.4 Laboratory Data and Miscellaneous Side Effects

During a 12-month trial with budesonide 100μg 4 times daily only 10 patients of 166 withdrew from the trial for drug-related reasons (unpublished data on file, Astra). The majority of these were related to adverse local reactions and two were due to depression. Most laboratory parameters were not significantly changed during follow-up although alkaline phosphatase was significantly increased, and leucocyte count and serum bilirubin were slightly but significantly decreased – these changes were of doubtful clinical relevance.

An isolated case of severe bronchoconstriction induced by a single puff (200μg) of inhaled bude-

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sonide has been reported (McGivern and Macfarlane, 1984). Challenge tests revealed appreciable bronchoconstriction to both budesonide and its propellants, but contaminants (from the aluminium can or rubber valve) may also be implicated. Another case report indicated that inhaled budesonide in a dose of two 50μg puffs twice daily may have been responsible for an episode of psychotic behaviour in a 5½-year-old girl being treated for secondary bronchial hyperactivity (Lewis and Cochrane, 1983). Steroid psychosis is well recognised, especially in patients on high dose systemic steroids, and in this instance the symptoms disappeared when the dosage was halved. The time course of events suggests budesonide was the causative agent although no rechallenge was performed for ethical and parental reasons and it remains possible that the propellants in the inhaler may have provoked the reaction.

6.2 Intranasal Budesonide

The most frequently reported adverse effects associated with the intranasal application of budesonide in patients with allergic or non-allergic rhinitis have been local reactions such as nasal stinging, throat irritation, dry nose and nasal bleeding.

In short term comparative studies in patients with seasonal allergic rhinitis, intranasal budesonide seemed to cause fewer side effects than the antihistamine dimethylphenindramine (especially dryness of the mouth, and drowsiness) [Munch et al., 1983], significantly less ($p < 0.02$) nasal irritation than flunisolide (Pipkorn and Geterud, 1984), and a similar incidence of minor transient reactions as beclomethasone dipropionate (Pipkorn, 1985b; Pipkorn and Rundcrantz, 1982) and sodium cromoglycate (unpublished trials on file, Astra). In longer term trials in patients with perennial rhinitis, the incidence of side effects has been low (Balle, 1982; Lindqvist et al., 1982, 1983; Pipkorn and Berge, 1983) and those laboratory parameters which were measured all remained within the reference range. In 2 of these studies the only adverse effects reported were a transient skin rash around the nose in 1 patient and nasal bleeding in 4 patients (Balle, 1982; Pipkorn and Berge, 1983). In all 4 studies, adrenal function remained normal as assessed by basal plasma cortisol concentrations and their response to tetracosactrin stimulation. In a 4-month placebo-controlled double-blind trial in 19 patients with nasal polyposis, intranasal budesonide produced a low incidence of mild transient side effects with no evidence of mucosal drying or crusting (Holopainen et al., 1982).

7. Dosage and Administration

7.1 Asthma

The recommended inhaled dosage of budesonide for the treatment of bronchial asthma in adults is individual. Initially it is normally 400 to 1600 μg/day divided into 2 or 4 administrations. The maintenance dose is also individual and should be the lowest dose which leaves the patient symptom free. In adults this is usually achieved with a dose of 200 to 400μg twice daily. In children with asthma the recommended regimen is 200 to 400 μg/day, divided into 2 or 4 administrations. There is evidence that a twice daily regimen may be less effective than 4 times daily administration when asthma is poorly controlled. As for all aerosolised corticosteroids it is important that the patient uses the inhaler correctly, since failure to respond has been correlated with poor technique (Newman, 1983). Inhalation through a spacer may prove to be clinically useful for a proportion of patients by augmenting the airways response and reducing the severity of candidiasis for any particular dose of budesonide. Special care should be observed in patients with pulmonary tuberculosis, fungal and viral infections of the airways, those transferring from systemic steroids, and in pregnancy.

7.2 Rhinitis

In the treatment of seasonal and perennial allergic rhinitis and vasomotor rhinitis the recommended budesonide dosage is 2 applications into each nostril morning and evening from a metered-dose aerosol delivering 50μg per actuation (400 μg/day). When a good response has been achieved the

dosage may be reduced to one application into each nostril morning and evening (200 μg/day). Results from continuous long term trials in children are currently not available. As with other corticosteroids the full effect of budesonide may not be apparent for a number of days and it is important that the patient understands that the treatment is not intended for rapid relief and that it must be used regularly.

8. The Place of Budesonide in Therapy

The results from studies conducted to date indicate that budesonide is an effective topical corticosteroid for the clinical management of asthma and rhinitis. However, as would be expected at this stage in its development, the extent of published therapeutic experience is limited, especially when compared with that of beclomethasone dipropionate – the most widely studied topical agent in these conditions.

In short term comparisons between usual doses of inhaled budesonide and inhaled beclomethasone dipropionate, no significant differences between the 2 treatments have been documented in adults with asthma of varying degrees of severity. Similarly, in most trials in children with asthma these 2 corticosteroids have been shown to be of similar efficacy, although in a short term study of 21 asthmatic children budesonide (inhaled with a spacer) was found to produce significant improvements in lung function compared with equal doses of beclomethasone dipropionate (inhaled with a standard actuator). Comparative trials in the high dose area are still required to clarify the effects of inhaled budesonide and inhaled beclomethasone dipropionate in patients with severe asthma. In patients with seasonal rhinitis intranasal budesonide has been shown to be as effective as intranasal flunisolide and intranasal beclomethasone dipropionate and more effective than intranasal sodium cromoglycate. Short term trials in patients with perennial rhinitis (with or without an allergic component) indicate that budesonide is superior to placebo in relieving nasal symptoms, and long term benefit has been consistently shown in the longer term published trials. In a single study of 19 patients with nasal polyposis, intranasal budesonide was significantly better than placebo in reducing the size and number of polyps and in relieving nasal symptoms.

Thus, budesonide appears to offer a safe and effective alternative in conditions where an inhaled or intranasal corticosteroid is indicated. However, its relative efficacy and tolerability compared with other corticosteroids needs further clarification in longer term studies.

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Authors' address: *Stephen P. Clissold*, ADIS Drug Information Services, P.O. Box 34-030, Birkenhead, Auckland 10 (New Zealand).

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